NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA337: Rifaximin for preventing episodes of overt hepatic encephalopathy

Original publication date:	March 2015
Review date	March 2018
Existing recommendations:	Recommended. To see the complete existing recommendations and the original remit for TA337, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list' without consultation.

2. Rationale

Recent clinical evaluations of rifaximin suggest that it remains an effective treatment option in this patient population. No new evidence was identified that would substantially change the recommendations in TA337.

3. Summary of new evidence and implications for review

The vast majority of the new evidence supports that rifaximin is an effective treatment option for reducing the recurrence of episodes of overt hepatic encephalopathy. New treatment options could be emerging in the next few years. One study suggested that a new technology in development, fecal microbiota transplant (FMT), was associated with lower hospitalisation risk and improved cognitive function in patients with recurrent hepatic encephalopathy, when compared with lactulose+rifaximin.[1]

Some new evidence, albeit limited, has emerged to support the assumption that hospital admissions are lower and utility values are higher in people who have had rifaximin: 2 of the main uncertainties outlined by the committee in the FAD. [2,3] There is still limited or no evidence relating to long-term mortality and remission specific utility values in this patient population.

In conclusion, there is no strong evidence to justify a review of the rifaximin guidance; moving it to the static list is the most appropriate option.

Has there been any change to the price of the technology(ies) since the guidance was published?

The price of the technology has not changed since the original guidance was published.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

There were three main uncertainties in the evidence:

- long-term mortality benefit associated with rifaximin
- the utility increment for patients in remission, and
- the effect of rifaximin on reducing hospital admissions.

A key area of uncertainty in this appraisal was the lack of long-term mortality data. The committee agreed that the greatest benefit of treatment would be expected in the early stages of treatment, and it noted that there was limited evidence to support long-term benefit. Although there is new clinical evidence evaluating the efficacy of rifaximin, long-term survival data is still not available. Therefore, the long-term impact of rifaximin on mortality remains uncertain.

There is new evidence to support the assumption that patients who have had rifaximin report higher utility values than patients that have not.[3,4] In the appraisal of TA337, there was uncertainty about the magnitude of the utility increment for patients in remission. The new evidence noted challenges in deriving utility values in patients with serious cognitive impairments.[3] Overall the assumption of higher utility values for patients who have had rifaximin seems clinically plausible; however the exact magnitude of this increment remains uncertain, and difficulties in estimating utility scores in this patient group presents a challenge for eliciting values in the future.

The extension study to the pivotal trial considered in the appraisal suggests that long-term treatment with rifaximin leads to a lower rate of hospitalisation compared to a placebo group.[5] This trend was supported by other evidence, however differences in levels of hospitalisation were not statistically significant.[2] The new evidence suggests that rifaximin is probably linked to a reduction in hepatic encephalopathy related hospitalisations. This new evidence supports the assumptions accepted in the previous consideration of the evidence, therefore there is no impact on the value proposition of rifaximin in this population and there is no need to review the guidance to account for this new evidence.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance

See Appendix C for a list of related NICE guidance.

Additional comments
None

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

The committee noted that comments received during consultation from the clinical expert that people with hepatic encephalopathy should be considered vulnerable adults. The Committee understood that this condition can have a substantial disabling effect, but considered that its recommendations do not discriminate on the basis of any characteristics protected under the equalities legislation. See Section 4.23 of the TA337 guidance.

GE paper sign off: Helen Knight, on behalf of Meindert Boysen, 28/03/2018

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of rifaximin within its licensed indication for the maintenance treatment of hepatic encephalopathy.

6. Current guidance

Rifaximin is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

The price of rifaximin when considered in the original guidance was £259.23 per 56‑tablet pack of 550 mg film‑coated tablets (excluding VAT).

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specified date	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50

Liver disease (2017) NICE Quality standard QS152

2. Details of new products

None.

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Indication: *"…reduction in recurrence of episodes of overt hepatic encephalopathy in patients aged 18 years or older".* Price: £259.23 per 56-tablet pack of 550 mg film-coated tablets (excluding VAT; British national formulary online [accessed December 2014])	No change to indication or price. (price checked using NHS Drug Tariff, January 2018).

4. Registered and unpublished trials

Trial name and registration number	Details
Efficacy, Safety, And Pharmacokinetics Of Rifaximin In Subjects With Severe Hepatic Impairment And Hepatic Encephalopathy NCT01846663; RFHE4043	Randomised, placebo-controlled trial n = 100 Currently recruiting Estimated completion date: May 2021 (primary outcome; June 2021 overall)

Appendix C

Trial name and registration number	Details
Randomised Controlled Trial of Mechanistic Effects of Rifaximin in Cirrhosis and Chronic Hepatic Encephalopathy NCT02019784; RIFSYS; KCH14-183_RIFSYS_V4.0; 2013-004708-20	Randomised, placebo-controlled trial n = 38 Completed in October 2016
Effect of Administration of Rifaximin on the Portal Pressure of Patients With Liver Cirrhosis and Esophageal Varices NCT02508623; 3250/AO/14; 2014-000102-35	Randomised, placebo-controlled trial with encephalopathy measured as a secondary outcome n = 60 Current status unknown. Estimated completion date: July 2017

Appendix D – References

1. Bajaj, J.S., Kassam, Z., Fagan, A., Gavis, E., Liu, E.J., Kheradman, R., Wang, J., Cox, J., Taylor-Robinson, S.D., Sikaroodi, M. and Alm, E., 2017. Fecal microbiota transplant using a precision medicine approach is safe, Associated with lower hospitalization risk and improved cognitive function in recurrent hepatic encephalopathy. Gastroenterology, 152(5), p.S906.

2. Bajaj, J.S., Barrett, A.C., Bortey, E., Paterson, C. and Forbes, W.P., 2015. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. Alimentary pharmacology & therapeutics, 41(1), pp.39-45.

3. Berni, E., Conway, P., Nanuwa, K. and Currie, C.J., 2014. Difficulty in establishing the impact of drugs on quality of life in cognitively impaired patients: Example of attempting to derive utility in patients treated with rifaximin-α for the reduction of recurrence of episodes of hepatic encephalopathy. Value in Health, 17(3), p.A182.

4. Kimer, N., Gluud, L.L., Morris, R.W. and Morgan, M.Y., 2017. Rifaximin for the prevention and treatment of hepatic encephalopathy: a systematic review with meta-analyses of randomised controlled trials. Journal of Clinical and Experimental Hepatology, 7, pp.S78-S79.

5. Mullen, K.D., Sanyal, A.J., Bass, N.M., Poordad, F.F., Sheikh, M.Y., Frederick, R.T., Bortey, E. and Forbes, W.P., 2014. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clinical Gastroenterology and Hepatology, 12(8), pp.1390-1397.