Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Rifaximin for maintaining remission from episodes of hepatic encephalopathy

Response to consultee and commentator comments on the draft scope

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Royal College of Nursing - Gastrointestinal Nursing Forum	Appears accurate and comprehensive.	Comments noted – no action required

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	Hepatic encephalopathy (also known as portal systemic encephalopathy) encompasses a spectrum of neuropsychiatric abnormalities seen in patients with established liver disease and is commonly associated with liver cirrhosis. Hepatic encephalopathy is the occurrence of confusion, altered level of consciousness and potentially coma due to the influence on the brain of toxic compounds that accumulate in the blood due to the inability of the cirrhotic liver to remove them from the blood, as would occur in healthy individuals. Approximately 70% of patients with cirrhosis present with subclinical or mild hepatic encephalopathy, and 23-40% may progress to a more severe form of the disease. One and three year survival rates of patients with cirrhosis, after experiencing an episode of hepatic encephalopathy, are 42% and 23% respectively Signs and symptoms of hepatic encephalopathy include personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity. Hepatic encephalopathy is associated with diminished health related quality of life, specifically related to physical and mental domains and is correlated to repeat hospitalisations.	Comment noted - no action required. Please note the background section is a brief description of the disease area, and written for the lay person (please refer to section 2.2.1 of the methods guide). This information is included within the 1st paragraph of the background section. Comment noted – No action required. As above, this information is included within the 3rd paragraph of the background section. Comment noted – No action required. As above, this information is included within the 1st paragraph of the background section.

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	In 1998 the 'Organisation Mondiale de Gastroentérologie Working Party' introduced a classification for hepatic encephalopathy. The group recommended dividing hepatic encephalopathy into three broad categories: A (acute liver failure), B (porto-systemic bypass without intrinsic liver disease) and C (cirrhosis). The three main hepatic encephalopathy 'types' widely referred to within group C are episodic hepatic encephalopathy, persistent hepatic encephalopathy and minimal hepatic encephalopathy. Hepatic encephalopathy can be graded using the Conn score (also called West Haven classification) in which higher scores indicate a higher severity, as follows: Grade 0: No personality or behavioural abnormality detected. Grade 1: lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition. Grade 2: lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behaviour, impaired performance of subtraction. Grade 3: somnolence to semi stupor but responsive to verbal stimuli, confusion, gross disorientation. Grade 4: coma (unresponsive to verbal or noxious stimuli). In 2011, the ISHEN classification system was proposed, but is yet to be fully adopted by the scientific community. It classifies patients as being 'unimpaired' (no clinical neurophysiological/neuropsychometric changes), having 'covert' hepatic encephalopathy (patients with minimal hepatic encephalopathy or hepatic encephalopathy with a Conn score of 1 as graded by the West Haven Criteria) or having 'overt' hepatic encephalopathy (patients with hepatic encephalopathy with a Conn score of 2,3 or 4 as graded by the West Haven Criteria)	Comment noted - no action required. As above, this information is included within the 2nd paragraph of the background section.

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	Key management goals for patients with hepatic encephalopathy are provision of supportive care, identification and removal / avoidance of precipitating factors, and administration of drugs. Pharmacotherapy is the mainstay of hepatic encephalopathy management. The major pharmacological treatments for hepatic encephalopathy target the production and absorption of bacterially-derived neurotoxins, particularly ammonia. A number of treatments are commonly used in the acute management of hepatic encephalopathy including non-absorbable disaccharides, such as lactulose, and unlicensed antibiotics such as including rifaximin-α, neomycin and metronidazole. Currently, there are no therapies licensed in Europe specifically for the reduction in risk of recurrence of overt hepatic encephalopathy episodes. However, lactulose is used as a therapeutic option for these patients.	Comment noted - no action required. As above, this information is included within the 4th paragraph of the background section. Comment noted - the background section has been updated to include this information.
The technology/ intervention	Royal College of Nursing - Gastrointestinal Nursing Forum	Yes	Comment noted – no action required

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	We are not in agreement with the current wording of the remit as it does not reflect the current proposed marketing authorisation. The technology is rifaximin (550mg BD). Pharmacotherapeutic group: intestinal, anti-infective - antibiotics - ATC code: A07AA11. Mechanism of action: Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis. 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. Rifaximin is administered orally. [redacted] In the pivotal study, 91% of the patients in the rifaximin and placebo groups were using concomitant lactulose. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Comment noted. No action required as the current remit states 'within its licensed indication', and therefore reflects the marketing authorisation. Comment noted - no action required. Please note the technology section is a brief description of the intervention, and written for the lay person. This information is included within the 1st paragraph of the technology section. Comment noted – the intervention has been updated, "in combination with lactulose" has been removed because the clinical trial included people who were not receiving lactulose. Treatment using rifaximin with lactulose has been included under 'other considerations'. The intervention will be appraised in line with the marketing authorisation.

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
Population	Royal College of Nursing - Gastrointestinal Nursing Forum	Yes. A further possible group has been identified as a sub group	Comment noted – no action required

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	We propose that the population is as defined by the SmPC: [redacted] **Questions for consultation:** Is rifaximin likely to be used to manage hepatic encephalopathy in people with a severe liver failure? Clinicians may use rifaximin to manage hepatic encephalopathy in people with severe liver failure as the SmPC states that rifaximin can be used in patients with hepatic impairment 'with caution'. 4.4 Hepatic Impairment: use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 (see section 5.2). 5.2 Hepatic impairment: Avaialble clinical data on patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. The increase in systemic exposure to rifaximin in patients with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in patients with cirrhosis. Therefore no dosage adjustment is recommended because rifaximin is acting locally. **Questions for consultation:** Should severity of hepatic encephalopathy be considered as a subgroup We do not believe that severity of hepatic encephalopathy should be considered as a subgroup. Clinical trial data was based on patients with cirrhosis who had prior episodes of hepatic encephalopathy.	Comment noted – population updated Comments from consultation have indicated that subgroups based on severity of liver failure may be clinically relevant. The 'other considerations' section of the scope states that effectiveness will be assessed by severity of liver failure 'if evidence allows'.

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	British Society of Gastroenterology	The population is defined as adults with liver cirrhosis who have had prior acute episodes of hepatic encephalopathy and are currently in remission. I think patients who also have minimal or subclinical hepatic encephalopathy also need to be included and the guidelines will need to include a section on how to diagnose minimal/subclinical hepatic encephalopathy.	Comments noted – This scope is concerned with the maintenance of remission from hepatic encephalopathy in patients who have prior episodes, and therefore patients with minimal or subclinical hepatic encephalopathy are outside of the remit of this scope. No changes required.
	Foundation for Liver Research	No mention is made in the populations to be studied of cases where encephalopathy has been accompanied or precipitated by other manifestations of clinical hepatic decompensation, namely bleeding or ascites, as it is common for more than one feature of clinical hepatic decompensation to be present. It will be important that the effect of Rifaximin on these is appraised as well as on hepatic encephalopathy as a known specific effect.	Comment noted – This scope is concerned with the maintenance of remission from hepatic encephalopathy, and although ascites and bleeding are features of hepatic decompensation and associated with hepatic encephalopathy, they are not a feature of the hepatic encephalopathy itself. No changes required
Comparators	Royal College of Nursing - Gastrointestinal Nursing Forum	Yes, they are used within this condition. The question regarding "should neomycin in combination with lactulose be considered as a comparator" is probably yes for a certain group of patients. Although not standard for most adults with hepatic encephalopathy (HE), some individuals with recurrent, perisitant HE will be on both to maximise any beneficial effects, this may be the group to focus that question towards.	Comment noted – no action required

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	Qs for consultation: Have the most appropriate comparators for rifaximin for the maintenance of remission from episodes of hepatic encephalopathy been included in the scope? Are the comparators listed routinely used in clinical practice? Should neomycin in combination with lactulose be considered as a comparator? Lactulose is the current standard of care and is routinely used in clinical practice. As per the SmPC and pivotal study by Bass et al, 91% of the patients on rifaximin and placebo were using concomitant lactulose Neomycin would appear not to be routinely used in clinical practice in the prevention of recurrence of hepatic encephalopathy in patients in remission, and should therefore not be included as a comparator.	Comment noted – please refer to section 2.2.4 of the methods guide. Here it states 'relevant comparators are identified, with consideration given specifically to routine and best practise in the NHS… relevant comparator technologies may also include those that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS'. As some patients do receive Neomycin to manage hepatic encephalopathy, Neomycin is considered a relevant comparator. No action required.

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	In the UK neomycin is licenced for hepatic coma but it is not licenced for the prevention of recurrence of hepatic encephalopathy. There is no clinical data to support the use of neomycin in the prevention of recurrence of hepatic encephalopathy in patients in remission. No controlled trials with neomycin have demonstrated equal or superior efficacy to lactulose. In addition the long term use of neomycin is also associated with the risk of ototoxicity and nephrotoxicitity. Additionally, based on Neomycin usage in Primary Care in England in 2011 (as sourced from Prescription Cost Analysis via the NHS Information Centre) there were only 29 prescriptions of Neomycin Tablets 500mg issued in the year 2011 and 2,320 tablets used. In summary we consider that the overall neomycin usage is minimal and as the data source does not specify an indication we believe that this usage is likely to be across a number of different indications. Therefore, for all the reasons stated above Neomycin should not be used as a comparator in the STA: Rifaximin for the maintenance of remission from episodes of hepatic encephalopathy.	Comment noted – please refer to section 2.2.4 of the methods guide. Here it states 'relevant comparators are identified, with consideration given specifically to routine and best practise in the NHS… relevant comparator technologies may also include those that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS'. As some patients do receive Neomycin to manage hepatic encephalopathy, Neomycin is considered a relevant comparator. No action required.
	British Society of Gastroenterology	The comparators used (Lactulose/Neomycin) are the ones used in clinic practice and are appropriate. Neomycin in combination with Lactulose should also be considered as a comparator.	Comment noted – Neomycin with lactulose has been added as a comparator.
	Foundation for Liver Research	Very few hepatologists now use neomycin although in practice it is a very useful agent. It is not used because of the perceived risks of ototoxicity and nephrotoxocity. The main comparator therefore will be lactulose	Comment noted – no action required

Appendix D – NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
Outcomes	Royal College of Nursing - Gastrointestinal Nursing Forum	Yes. The nature of reporting grades of HE remains subjective to the individual assessing them. The use of the west haven criteria is important, however across a large section of healthcare professionals it may be difficult to establish rigour as they will grade HE differently. Needs to have very specific parameters and possibly combine with an objective measure such as serum ammonia levels (although they do not always correlate either to severity of HE!)	Comment noted – no action required as the method of measuring the progression of HE, and grade, is not specified within the scope. The methods used will be reviewed as part of the appraisal process.

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Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	The clinical programme supporting the hepatic encephalopathy indication for rifaximin was designed to support regulatory approval with the FDA (as an orphan indication) and included endpoints of relevance to this disorder from this standpoint. (Bass N, Mullen K, Sanyal A, Poordad F, Neff G, Leevy C, et al. Rifaximin treatment in hepatic encephalopathy. New England Journal of Medicine. 2010;362(12):1071). Disease progression to more severe grade of hepatic encephalopathy 'Disease progression to more severe grade of hepatic encephalopathy' was not one of the endpoints / outcomes assessed in the main pivotal study by Bass et al and therefore we are not able to determine the effect of rifaximin on this endpoint. We believe that, for this reason, this should be removed from the scope. Frequency of hospitalisation, and time until next hospitalisation In the pivotal study by Bass et al, the main secondary endpoint was not the 'time until next hospitalisation' but the 'time to first hepatic encephalopathy related hospitalisation'. This is because the original study design resulted in patients who experienced breakthrough episodes of hepatic encephalopathy or hepatic encephalopathy related hospitalisations discontinuing treatment at the time of the event.	Comments noted. Please refer to section 2.2.6 of the methods guide. It states that 'for the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant'. The outcomes listed within the scope are considered clinically relevant. Transplant (time to, and frequency) was not considered a clinically relevant measure of hepatic encephalopathy due to the number of factors, other than hepatic encephalopathy, that impact transplant (availability, eligibility factors) and therefore these have been removed as outcomes.

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	6 months data is available for both the rifaximin and placebo groups for 'time to first hepatic encephalopathy related hospitalisation' Frequency of recurrent acute episodes of hepatic encephalopathy and time to next episode In the pivotal study by Bass et al, the main primary endpoint was not the 'time to next hepatic encephalopathy episode' but the 'time to first breakthrough episode of hepatic encephalopathy'. This is because the original study design resulted in patients who experienced breakthrough episodes of hepatic encephalopathy discontinuing treatment at the time of the event. 6 months data is available for both the rifaximin and placebo groups for 'time to first breakthrough episode of hepatic encephalopathy'' Rate of liver transplantation/ Time to liver transplantation Neither 'rate of liver transplantation' nor 'time to liver transplantation' were endpoints / outcomes assessed in the main pivotal study by Bass et al and therefore we are not able to determine the effect of rifaximin on these endpoints. Questions for consultation: Given that Rifaximin-α does not act directly on the liver, is it appropriate to include the liver transplant outcomes? In addition, as rifaximin does not act directly on the liver we do not believe that it is appropriate to include any 'liver transplant' outcomes in this scope.	Comments noted. Please refer to section 2.2.6 of the methods guide. It states that 'for the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant'. The outcomes listed within the scope are considered clinically relevant. Transplant (time to, and frequency) was not considered a clinically relevant measure of hepatic encephalopathy due to the number of factors, other than hepatic encephalopathy, that impact transplant (availability, eligibility factors) and therefore these have been removed as outcomes.

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	Mortality The pivotal study by Bass et al was not powered to look at differences in mortality. Consequently, mortality was not one of the endpoints / outcomes of the study and therefore we are not able to determine the effect of rifaximin on this endpoint. 'Death' was however recorded as an adverse event / reason for discontinuation from the study and therefore could be included as part of the 'adverse events' in this STA Adverse effects of treatment In the pivotal study by Bass et al, analysis of adverse events and serious adverse events showed that there was no difference between the rifaximin and placebo groups over a 6 month period. Mortality should be included as part of the 'adverse events' in this STA Health-related quality of life Whilst we agree with this in principal, we are unable to provide EQ-5D data as this was not collected during the pivotal study by Bass et al. Chronic Liver Disease Questionnaires (CLDQ) and SF-36 were however used during the study to collect data on Quality of Life (QOL) at specific time points. Due to the design of the study, QOL was not assessed if a patient experienced an episode of breakthrough hepatic encephalopathy or hospitalisation, and patients who did experience an event (hepatic encephalopathy episode or hospitalisation) discontinued treatment. Therefore no further assessments were taken.	Comments noted. Please refer to section 2.2.6 of the methods guide. It states that 'for the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant'. The outcomes listed within the scope are considered clinically relevant. Transplant (time to, and frequency) was not considered a clinically relevant measure of hepatic encephalopathy due to the number of factors, other than hepatic encephalopathy, that impact transplant (availability, eligibility factors) and therefore these have been removed as outcomes.

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Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	The only data available on QOL is the impact of the intervention on QOL versus placebo during remission (as calculated by time weighted averages of differences in CLDQ). [redacted]	Comments noted – no action required.
	British Society of Gastroenterology	The outcomes suggested are appropriate. To the question whether it is appropriate to include liver transplant outcomes, given that hepatic encephalopathy is one of the reasons for liver transplantation, it is reasonable to include the rate of liver transplantation and the time to liver transplantation in the outcomes.	Comment noted - transplant (time to, and frequency) was not considered a clinically relevant measure of hepatic encephalopathy due to the number of factors, other than hepatic encephalopathy, that impact transplant (availability, eligibility factors) and therefore these have been removed as outcomes
Outcomes	Foundation for liver research	In patients with the first manifestations of encephalopathy, liver transplantation may be long delayed ie for a period of years. Time to liver transplantation is not therefore a good outcome measure. Furthermore, there are many influences leading to transplantation in an individual case apart as well as encephalopathy. Encephalopathy alone is rarely an indication for liver transplantation.	Comment noted - transplant (time to, and frequency) was not considered a clinically relevant measure of hepatic encephalopathy due to the number of factors, other than hepatic encephalopathy, that impact transplant (availability, eligibility factors) and therefore these have been removed as outcomes

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Section	Consultees	Comments	Action
	British Liver Trust	this treatment could potentially have a very positive effcet on the patient's, and their families, quality of life. Current treatments cause bloating, diarrhoea, urgency to defaecate and flatulance (and sometimes constipation / lazy bowel) - this treatment would greatly reduce these side effects	Comment noted – no action required.
Economic analysis	Royal College of Nursing - Gastrointestinal Nursing Forum	It needs to be longitudinal as long as clinical condition and severity of liver failure will allow.	Comment noted – no action required

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	The reference case stipulated that the cost effectiveness of treatment should be expressed in terms of the incremental cost per quality adjusted life year Whilst we agree with this in principal, we are unable to provide EQ-5D data as this was not collected during the pivotal study by Bass et al. Chronic Liver Disease Questionnaires (CLDQ) and SF-36 were however used during the study to collect data on Quality of Life (QOL) at specific time points. Due to the design of the study, QOL was not assessed if a patient experienced an episode of breakthrough hepatic encephalopathy or hospitalisation, and patients who did experience an event (hepatic encephalopathy episode or hospitalisation) discontinued treatment. Therefore no further assessments were taken. [redacted] The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. We are open to using a lifetime time horizon. However additional data / studies may be required in order to construct a model with a 5 year or lifetime horizon.	Comments noted – no action required

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Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	As per our SmPC: The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction. Costs will be considered from an NHS and Personal Social Services perspective. We agree that costs should be considered from an NHS and Personal Social Services perspective.	Comments noted – no action required
Equality and Diversity	Royal College of Nursing - Gastrointestinal Nursing Forum	No specific comments	Comment noted – no action required.
	British Liver Trust	this treatment would increase the equality of people with liver related encephalopathy increasing treatment options and better quality of life as with HIV encephalopathy etc	Comment noted – no action required.

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Section	Consultees	Comments	Action
Other considerations	Norgine Pharmaceuticals Limited	If evidence allows the effectiveness will be assessed by severity of liver failure. In the pivotal study by Bass et al, a subgroup analysis was undertaken within MELD scores and rifaximin was shown to be effective across all MELD scores. This suggests that effectiveness is not dependent on severity of liver failure. However, due to small 'n' numbers in the MELD 19-24 scores it was not possible to demonstrate significance. There is no data to support the use of rifaximin in patients with MELD score higher than 25. Guidance will only be issued in accordance with the marketing authorisation. We are in agreement with this and we are currently awaiting a decision on the wording of the proposed licence and SmPC for rifaximin.	Comments noted – no action required
	British Society of Gastroenterology	Even though there may not be much evidence of the use of Rifaximin in severe liver failure, I think it is reasonable to include the use of Rifaximin in the management of patients with severe liver failure as currently both Lactulose and Neomycin are used in this respect. There are no other subgroups of people that need to be included and I do not think that severity of hepatic encephalopathy should be considered as a subgroup but this is open for discussion. The provisional list of organisations who have been invited to participate in the appraisal is comprehensive and appropriate.	Comments noted – no action required.

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Section	Consultees	Comments	Action
Questions for consultation	Royal College of Nursing - Gastrointestinal Nursing Forum	Yes, there have been favourable reports from healthcare professionals who have cared for this patient group receiving named patient rifiximin. It is timely for it to be considered now. It could improve the patient's quality of life substantially. The burden on families/ carers could be significantly reduced and also improved patient safety.	Comments noted – no action required

Section	Consultees	Comments	Action
	Norgine Pharmaceuticals Limited	Health related benefits / management: The prevention of episodes of hepatic encephalopathy is an important goal in the treatment of patients with liver disease. As discussed earlier, lactulose is the current standard of care and is routinely used in clinical practice. However there is no clinical evidence to support the use of lactulose in the prevention of recurrence of hepatic encephalopathy in patients in remission. The pivotal study by Bass et al is the first study to examine the protective effect of rifaximin against breakthrough episodes of hepatic encephalopathy, rather than its effect in the treatment of acute, overt symptoms over a 6 month period. Bass et al shows the superiority of rifaximin therapy plus lactulose over treatment with placebo plus lactulose, and a significant treatment effect was noted within 28 days after randomisation. Rifaximin therapy reduced the risk of hospitalisation involving hepatic encephalopathy, reflecting the clinical significance of the efficacy findings. In summary, there is currently a large unmet need for effective treatments to manage patients with cirrhosis who experience hepatic encephalopathy. Rifaximin has been shown to significantly reduce breakthrough hepatic encephalopathy episodes and hospitalisations, compared with placebo (approximately 90% were also taking lactulose) in patients in remission from hepatic encephalopathy associated with hepatic cirrhosis, therefore offering the potential to improve health related outcomes. Rifaximin appears to offer a step change in the management of the condition.	Comments noted – no action required

Section	Consultees	Comments	Action
		Benefits not included in the QALY: We believe that there are potential substantial health related benefits that are unlikely to be included in the QALY calculation. These include the impact on the following health related QOL domains as demonstrated by the CLDQ; abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry. These also include the impact on the health and quality of life of carers. Bajaj et al. (2011) interviewed caregivers of two sets of patients with cirrhotic liver disease – those with hepatic encephalopathy and those without. The results show that caregivers of patients with hepatic encephalopathy report a significantly higher burden than caregivers of patients without hepatic encephalopathy. It is likely that a reduction in hepatic encephalopathy episodes and hospitalisations will have a beneficial effect on carer burden and consequently on their health related quality of life, although this has not yet been assessed as part of a formal study.	Comment noted – no action required. This will be considered within the appraisal process.
Additional comments on the draft scope.	Royal College of Nursing - Gastrointestinal Nursing Forum	This is a timely opportunity to review the effectiveness of rifaximin	Comment noted – no action required

The following consultees/commentators indicated that they had no comments on the draft scope

Department of health

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rifaximin for maintaining remission from episodes of hepatic encephalopathy

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Remove National Hepatitis C Network from patient/carer group consultees	NICE Secretariat		Removed	This organisation has disbanded.