Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	academic hepatologist Professor[redacted]
Location	England
Conflict	yes
Notes	I have written an article on Hepatic encephalopathy sponsored by the company but as yet not accepted for publication
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	independent of quality of life benefits reducing hospital admissions is in itself a surrogate marker of improved quality of life Â in addition the quality of life of carers needs addressing
Section 2 (The technology)	My use of both the 200mg formulation and 550mg formulation has resulted in no side effects approx 40 patients to date Â very well tolerated
Section 3 (The manufacturer's submission)	The number of transplants is correct.It is rare to transplant for recurrent episodic encephalopathy per se unless liver dysfunction severe.It should be understood that encephalopathy is not part of either MELD or UKELD which provide minimum listinf scores for transplantation.Thus patients are cannot be listed and will have low priority if recurrent encephalopathy is their problem Â and liver function reasonably maintained
Section 4 (Consideration of the evidence)	seems reasonable and accurate
Section 5 (Implementation)	ok
Section 6 (Proposed recommendations for further research)	none
Section 7 (Related NICE guidance)	this date is far too long into the future It should be as soon as company can deliver the added information requested.The drug works well in clinical practice on top of lactulose .For some patients with recurrent admissions it has transformed their daily life and that of their families.
Section 8 (Proposed date of review of guidance)	There is not one gastroenterologist nor hepatologist Â shame on yo all surely you need one here!!!
Date	12/18/2013 3:17:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	Hepatic Encephalopathy is an area where there have been few advances in the last 20 years since Sheila Sherlock made her first observations. The emergence of fatty liver disease as an

	important and common cause for cirrhosis has increased the number of patients presenting with intractable encephalopathy as a complication of portal hypertension. This is a common presentation of advanced fatty liver disease. A large number of these patients have comorbidity that makes them unsuitable for definitive therapy such as transplantation and therapeutic options such as Rifaximin provide symptomatic control and have very clearly reduced hospitalisation rates. The alternative is too desperate to consider, and the impact on patients, families and carers is enormous. Many patient's (and their family's) lives are ruined by intractable encephalopathy. The increased use of TIPS shunts for refractory variceal bleeding has created another cohort of (often young) patients who are often severely disabled with chronic encephalopathy. Many of these patients are inelligible for transplantation due to ongoing addiction issues with alcohol etc. Their use of hospital resource as clinicians battle to control the encephalopathy is enormous. Just this morning i have been emailed about a patient in Wales who has encephalopathy from a TIPSS put in to control variceal haemorrhage, but is unsuitable for a transplant. The patient has been semi-comatose and in hospital for 2-3 weeks already and has now lost all ability to manage for themselves independently. The cost of a Rifaximin prescription here is small compared to Â paying a lifetime of nursing home costs to care for a 48 year old man who can no longer toilet himself. Alternatives to Rifaximin are lacking a strong evidence base and more difficult to use, with a worse side effect profile than this drug. In addition this antibiotic has robust trial data published in a premier medical journal that supports its efficacy and suggests that regular prescription will reduce hospitalisation. In the UK hospitalisation with complications of liver disease yields some of the longest inpatient stays of all indications for admission, so avoidance of admission and community treatment is all important. I would ask that the NICE committeee takes this into account in making thier judgement. Liver disease is now the 5th most common cause of death in the UK and the 3rd most common cause of death under the age of 65ys. Rates of liver cirrhosis and mortality are rising and the morbidity and associated costs of treatment are enormous. Rifaximin is one tool that might help reduce the disabiity associated with chronic encephalopathy and prevent sequelae of chronic brain injury. There really Â is no realistic alternative to this drug at present.
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	Most experts in the field would agree that notwithstanding the usual nit-picking, the Bass study provides a much more robust platform for decision making than a NICE committee usually has to consider (As perceived by someone who already has had experience of a NICE appraisal!)

Section 8 (Proposed date of review of guidance)	Ther eis not one member of the specialist team with any real world experience of manging liver disease, the complications of liver disease, or encephalopathy. Although you have taken expert evidence I suspect there is a real lack of practical knowledge, and I suspect this has impaired your decision making. Context is vital here.
Date	12/18/2013 1:41:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Very poor decision
Section 2 (The technology)	OK
Section 3 (The manufacturer's submission)	ok
Section 4 (Consideration of the evidence)	Poor decision based on benefits to patients and less load on in-patient burden and even abroggating the nered for transplantation
Section 5 (Implementation)	agree
Section 6 (Proposed recommendations for further research)	n/a
Section 8 (Proposed date of review of guidance)	MOre Hepatologist required in my opinion
Date	12/18/2013 1:41:00 PM

Name	[redacted]
Role	NHS Professional
Other role	Clinical Lead for Hepatology, Portsmouth Hospitals NHS Trust
Location	England
Conflict	no
Notes	I received payment for attending an advisory board for Norgine.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Rifaximin has clearly been shown to be effective reducing relapse of hepatic encephalopathy (HE). Hopefully, the QoL analysis will be forthcoming but those of us using the drug in clinical practice have seen considerable gains in QoL for patients and their carers. The scenario analysis of diminishing mortality benefit presented by NICE looked over-simplistic and the optimistic survival data

	did not accurately reflect prognosis of decompensated cirrhosis as reported in several large hepatology studies.
Section 2 (The technology)	The technology summary seems accurate, although the listed "common" adverse reactions are difficult to attribute to rifaximin and are certainly not common in clinical practice. Several of the adverse effects listed are more likely manifestations of chronic liver disease or concommitant lactulose use.
Section 3 (The manufacturer's submission)	I would support the manufacturer's contention that the comparison should be with lactulose rather tha neomycin. Neomycin is very rarely used due to concerns about absorption and side effects particularly nephrotoxicity. Lactulose itself has considerable adverse effects and diminshes quality of life through the incidence of diarrhoea, flatulence and abdominal discomfort.
Section 4 (Consideration of the evidence)	Rifaximin has been widely used throughout Europe for many years and several of us in the UK have built up clinical experience using the agent. Since 2010, I have treated around 50 patients with chronic HE in Portsmouth and have found that the agent does reduce hospitalisation. We recently submitted an abstract to the European Association for the Study of the Liver (EASL) annual meeting documenting our experience. We included all patients commenced on rifaximin between May 2010and November 2012.Data were analysed for 6 months prior to rifaximin and at 3, 6 and 12 months later. There were 42 patients, 62% male, mean age 59. Â Mean baseline scores were Child's-Pugh 9.4 (SD 2.1), MELD 15.0 (SD 7.9), UKELD 51.2 (SD 5.1). Survival at 3, 6 and 12 months was 78%, 67% and 62%. There was significant reduction in Child's-Pugh at 3 and 6 months (p< 0.01) but not 12 months and no change in MELD or UKELD. Comparing 6 months pre/post rifaximin, hospitalisation days fell from 233 to 143, a mean of 5.6 per patient, representing ?1,829 tariff costs. Admission episodes fell from 25 to 11.
Section 5 (Implementation)	N/A
Section 6 (Proposed recommendations for further research)	N/A
Section 7 (Related NICE guidance)	This date seems too far ahead and, given the lack of alternatives to rifaximin, an earlier review would be welcomed.
Section 8 (Proposed date of review of guidance)	Surprising lack of liver disease experts on the panel.
Date	12/18/2013 8:24:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	Scotland
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In our centres experience Rifaximin reduced the number of hospital admissions, backed up by our audit data, and anecdotally has a quality of life benefit to our patients.
Section 2 (The technology)	We have found that Rifaximin is very well tolerated, and perhaps compliance is improved and has in part a role to play in its efficacy (compare with the side effects of lactulose)
Section 3 (The manufacturer's submission)	We audited our cohort of patients on Rifaximin and found that it reduced the number of hospital admissions and therefore inpatient costs/complications following the introduction of Rifaximin in our patients.
Section 4 (Consideration of the evidence)	Aim: To evaluate the clinical benefit of using Rifaximin in end stage liver disease patients with hepatic encephalopathy as an adjunct to currently used modalities. Â Methods: Rifaximin use was audited in a single university hospital. An electronic database of patients who were receiving long-term treatment for hepatic encephalopathy was obtained. Records were reviewed manually. Â Outcomes were total number of admissions with and without treatment and total length of stay per admission. Â Data was divided into patient months prior and after commencement of Rifaximin. Outcomes were compared and analysed for statistical significance using Mann-Whitney U Test. Results: 16 patients were selected. Mean age was 61 (range 42 to 73) years. Four had previously undergone TIPSS procedures. Hepatic encephalopathy was secondary to alcoholic liver disease (n=7), Non-Alcoholic Steatohepatitis (n=6), Hepatitis C (n=1), Autoimmune Hepatitis (n=1) and iatrogenic post splenic artery rupture repair Â (n=1). Patients had a combined 233 months on Rifaximin and 203 months off. The total number of admissions decreased from 2.2 per patient (range 0-11) prior to and 1 (range 0-8) after starting rifaximin ($p < 0.05$), average length of stay was 7.6 nights (1-58) and 4.9 respectively (1-26) ($p < 0.05$). This equates to 1.35 nights per month and 0.29 nights per month respectively for each patient prior to and following commencement of treatment.
Date	12/17/2013 10:47:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	on norgine advisory bpard
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Scotland has already taken on board a commitment to use rifaximin for the treatment of hepatic encephalopathy - Whilst there may not be an existing robust evidence base in clinical practice patients respond well to this therapy.Hepatic encephalopathy can have devastating effects for both patient and carers with frightening, often variable symptoms of disease and significantly overall reduced quality of life. This is costly to the NHS, not only in terms of hospital admissions but also in home visits by professionals such as GPs, practice nurses and paramedics.
Section 2 (The technology)	Rifaximin is a well tolerated drug and out of 18 patients in Cornwall studies only one patient complained of mild abdominal pain and others experienced no side-effects. From a clinical perspective rifaximin clearly improves patient and carers quality of life and reduces hospital admissions.
Section 3 (The manufacturer's submission)	It is difficult to quantify the cost of living day in and out with a disease such as HE- not only the acute service but also primary care services. Competing therapies include lactulose which is generally not well tolerated in high dosages and can bring on a myriad of problems and restrictions to lifestyle. Neomycin can be particularly nephrotoxic and it is vitally important to protect the liver patient also from a renal perspective.
Section 5 (Implementation)	At present this drug is being used in clinical practice.
Date	12/17/2013 8:51:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The department of gastroenterology at [redacted] has been using Rifaximin for just over a year now reflecting the Bass et al paper (N Engl J Med. 2010;362(12):1071)showing a reduction in hospitalisation with encephalopathy. We have found it effective and operate a database that reviews the efficacy on every patient. Even when efficacious our policy has been to withdraw it at 6 months and reassess. Our data has been very positive and was submitted as an abstract to the DDW 2014. We would be keen to see NICE approve rifaximin for the prevention of hepatic encephalopathy and would be more than happy to share our data.

Section 2 (The technology)	No comments
Section 3 (The manufacturer's submission)	No comments
Date	12/17/2013 7:57:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	I have been a member of the Norgine advisory board since 2012
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	As c clinical nurse specialist in hepatology I have worked with patients with ESLD for the last 30 years (previously as a ward sister on a liver unit) Hepatic Encephalopathy (HE) is one of the most challenging complications of end stage liver disease. It is often under diagnosied because it can be difficult to detect in a clinic visit when it is minimal and patients and their families are often impacted by it in terms of personality changes, loss of memory, difficulty in concentrating on simple tasks which may lead to loss of their occupation. When it becomes more overt then their families may have to become their carers and this can cause serious fiancial difficulties. A common comment from a carer is " this is not the man/woman I married" due to their personality changes people can become agressive and difficult to manage refusing to take medications or to eat. All of which add to their decline. In patients who have failed lactulose therapy with repeated admissions and may have complex admissions as they can be difficult to manage in a ward where they are not compliant with treatment as well as being agressive and at risk of hurting themselves by trying to get out of bed and leave the ward. In some cases they may need to be intubated and ventilated in Intensive Care in order to deliver care and for their own safety. Rifaximin reduces admissions, improves the patients quality of life and those of their family and carers as well, enabling them to be compliant with their nutrition and other medications to treat their liver disease. There has been no other treatment that has been this exceptional in the maintenance treatment of HE. It has slowed down patients progression of their disease and it would be a back ward step in the care of thses patients if NICE didnt approve this medication for this indication. Chronic liver disease can be a very slowly progressive illness with many complications alongside HE such as variceal bleeding, spontaneous bacterial pertionitis, malnutrtion which may require repeated admissions and outpatient clinic visits and rifaximin is clearly able to reduce HE admissions while improving quality of life.
Date	12/17/2013 10:49:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In clinical practice this is an invaluable drug to keep patients out of hospital, and in the case of post TIPS encephalopahty prevent closure of the shunt (and hence life-threatening GI bleed). I am using it currently in 3 patients who would otherwise require transplantation for encephalopathy. Quality of life improvements on this drug are profound and should not be underestimated by the appraisal committee.
Section 4 (Consideration of the evidence)	Venous ammonia levels, asterix & fatigue scores, SF-36 scores and Epworth Sleepiness scores are not valid end-points in determining the severity of encephalopathy. As we have no better hard end-points re-admission rates should be taken as gold-standard evidence.
Date	12/13/2013 8:54:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	I have been a member of an advisory board for the manufacturer
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There is no validated QoL measure for hepatic encephalopathy but there is obvious major clinical benefit seen in patients using the drug. I have no dubt it works and provides a major improvement on QoL for pateints with encepahlopathy.
Section 2 (The technology)	no comments
Section 3 (The manufacturer's submission)	This in my view is overly complex and misses teh point. Do clinicians see patients treated with this drug who's quality of life is revolutionised? Yes. If patients take it do they avoid hospitalisation-yes. The magnitude of benefit may be debated but it is a major change in apositiev direction for patients and should be supported.
Section 4 (Consideration of the evidence)	see previous comments. This drug works and there is nothing else. It will be cost saving even taking the worst case.
Section 5 (Implementation)	no comments
Section 6 (Proposed recommendations for further research)	no comments

Section 7 (Related NICE guidance)	no comments
Section 8 (Proposed date of review of guidance)	no comments
Date	12/12/2013 11:01:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	I have had several patients with crippling, resistant chronic encephalopathy whose lives, and those of their families have been transformed for the better by using rifaximin. Â It is a very useful drug for encephalopathy. Â My main concern is that its value may be eroded by its more trivial use for travellers' diarrhoea, which may lead to widespread resistance of bacteria.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In practical hepatology, it is a very useful drug, and transforms the lives of patients and their relatives/carers.
Section 2 (The technology)	It is well tolerated in my experience.
Section 3 (The manufacturer's submission)	The manufacturer's evicence largely reflects experience with the drug in clinical practice. Â We only use it when there has been overt clinical encephalopathy which is non-responsive to lactulose.
Section 4 (Consideration of the evidence)	Chronic hepatic encephalopathy is demoralising and very expensive in use of NHS resources, as well as the time of carers. Â Rifaximin is the first breakthrough in this area for years, and may provide a useful bridge to other treatments such as transplant. With a hugely rising trend of liver disease in the UK, we badly need this drug to be available.
Date	12/12/2013 8:29:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is going to take a long time to get this data. Many hepatologist have been using Rifaximim and have information on utility such as reductions in inpatients stays and admissions and need for community services, but unlikely to have formal quality of life assessment. This evidence should be assessed by appraisal committee.
Section 2	I have found Rifaximim very well tolerated in amjority of patients

(The technology)	with very few side effects.
Section 3 (The manufacturer's submission)	The trial data is not exhaustive and company has tried to extract as much evidence of benefit that it can from studies. No data on high MELD patients who may gain significant benefit from rifaximim
Section 4 (Consideration of the evidence)	well considered
Section 5 (Implementation)	OK
Section 6 (Proposed recommendations for further research)	N/A
Section 7 (Related NICE guidance)	Rifaximim has already been used in clinical practise with real life benefits to improve patients quality of life, frequency of admissions, dependency. The delay to review will have significant impact on patients who are and may be in next deriving benefit. Also as increasing prevalence of chronic liver disease due to alcohol and obesity the loss of Riaximim from therapeutic options will increase burden on secondary care with prolonged admissions with encephalopathy. An earlier review would be important
Section 8 (Proposed date of review of guidance)	Needs more hepatology clinician imput
Date	12/10/2013 4:54:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a Gastroenterology Consultant, who routinely treats patients with encephalopathy, I am dissapointed that NICE are 'minded' not to approve Rifaximin. Â This is a very dififcult condition, with limited treatment options and a considerbale health impact. Â To prevent Rifaximin use would negatively impact on our ability to treat patients, as for many there are no real alternatives.
Date	12/10/2013 12:56:00 PM

Name	[redacted]
Role	
Other role	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1	HE results in significant poor quality of life, attendance in OP,

(Appraisal Committee's preliminary recommendations)	extended length of stay in hospital and frequent admission to hospital. It is an indication for liver transplantation. Therapies are dietary and lactulose, both significantly limited in efficacy and tolerability. lactulose in particular has poor data for its efficacy in HE and is associated with poor compliance due to sickly taste and associated increased frequency of bowel motions which is difficult to maintain in the long term. Using liver transplantation to treat HE is not cost effective and as organ availability continues to remain static alternative therapies need to be considered. Rifaximin appears to be a major step forward. It seems severe to consider a need to change QALY data scores. It is our experience and audit experience from Bristol and several centres in the UK that length of stay and need for admission is significantly reduced by the use of this drug. I would urge NICE not to dismiss this important medication and if costs are a concern recommend review of efficacy after one month of the medication being prescribed and if there is no clinical or objective improvement then it should be discontinued.
Date	