Dear NICE Appraisal Committee,

As one of the clinical advisors who served on the committee during the recent review on May 30th, I wanted to write to express my dismay as a clinical hepatologist and expert in hepatic encephalopathy at the preliminary committees' recommendation that rifaximin alpha is not recommended within its marketing authorisation, that is, for reducing the recurrence of overt episodes of hepatic encephalopathy in people aged 18 years or older. Without wishing to repeat the information which I provided to the committee at the meeting, I wanted to emphasise just how clinically efficacious this drug is in treating this debilitating chronic condition.

To put this into perspective, liver cirrhosis is now the fifth commonest cause of death in the United Kingdom. Hepatic encephalopathy is one of the complications that arises following the development of liver cirrhosis and can impact on up to 80% of all patients who have liver cirrhosis. Furthermore, up to 40% of these patients will go on to develop overt episodes which will either lead to a chronic debilitating condition which impairs their neurocognitive function, in a not dissimilar way to dementia, and/or results in repeated admissions to hospital when not uncommonly, patients may be required to be cared for in high dependency or intensive care facilities resulting in immense resource utilisation for the NHS. Patients who previously contributed to their communities and paid tax are frequently no longer able to work, drive a car and are reliant on their families and friends to care for them. A good example perhaps is of a 39-year-old man that I was referred in [redacted] with chronic hepatic encephalopathy that resulted in five hospital admissions of an average duration of 10 days over six months. This man was previously extremely highly functioning, having attained a degree [redacted] and was halfway through a [redacted] Ph.D. at [redacted]. He was employed as a [redacted] in a large global [redacted] company. He was also a father of four children under the age of 10. He developed non-alcoholic fatty liver disease which led to his cirrhosis. His symptoms of encephalopathy first began quite insidiously when he began to forget the names of his children. He had to abandon his Ph.D. and job and began claiming benefits for his family. The overt episodes of hepatic encephalopathy would typically begin following the development of constipation or a minor infection and would lead to him becoming confused, aggressive and incontinent of urine. He was commenced on the usual standard of care for his encephalopathy (lactulose at high dose) but this did not reduce his symptoms or the number of admissions to hospital. I saw him in my specialist hepatic encephalopathy clinic and commenced him on trial of rifaximin which within four weeks simply changed the life of him and his family. Since commencing the medication 18 months ago, he has had no further hospital admissions and is now considering taking up his studies on a part-time basis again. This is one example of over 100 patients that I have successfully treated in my specialist hepatic encephalopathy clinic with rifaximin. All of these patients were either in tolerant of lactulose or had no beneficial effect.

A typical admission to a high dependency unit within the hospital for a patient with severe hepatic encephalopathy costs on average over £50,000 for a median five day stay. Furthermore, these patients are frequently readmitted often within 30 days and therefore pose a huge resource burden on the NHS in addition to that of their caregivers, many of whom also have to give up work.

As I see it, there is no doubt of the clinical efficacy of rifaximin however I feel that the interim decision of the committee reflects the failure of the manufacturer to demonstrate a robust reduction in short and long-term mortality which has resulted in a flawed cost-effectiveness calculation. One problem is that we only have one good quality randomised controlled trial from the US which only lasted six months and therefore did not provide a good platform in which to perform a robust cost effectiveness model. A longer term clinical trial is therefore needed in the UK to provide a more robust data set to make such predictions. However, I have no doubt as a clinical hepatologist and expert in hepatic encephalopathy who also speaks on behalf of my colleagues in

the Liver Section of the British Society of Gastroenterology, that the hepatology community have no doubt that this drug is not only clinically efficacious but offers significant cost reductions by way of reduction in hospital readmission rates. Indeed, I'm currently in the process of collating a large audit dataset containing 400 patients from over 10 liver centres in the United Kingdom that I hope will demonstrate the clinical efficacy of the drug, reduction in hospital admission rates and potentially a positive effect on reducing mortality although I am unlikely to be able to present this dataset to you within the next three months as we are still collecting follow-up data. I therefore in the meantime want to speak on behalf of the patients and their families who have benefited from this relatively cheap drug which has very little in the way of adverse side-effects. I have even witnessed two patients being de-listed for liver transplantation (for the indication of hepatic encephalopathy) which has enormous implications on the availability of scarce your organs in United Kingdom as well as additional reduction in substantial costs.

I therefore implore the committee to reconsider their preliminary recommendation on the basis of the drugs proven clinical efficacy on the condition that further data is obtained from the manufacturer and clinical hepatology community that may better demonstrate any cost-effectiveness and mortality benefit.

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Yours sincerely,

Debbie Shawcross

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