

**Non-formulary Criteria for Use: Rifaximin for Treatment of Hepatic Encephalopathy  
in Cirrhotic and Post-transplant Patients**  
**VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel**  
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*The following recommendations are based on current medical evidence. The content of the document is dynamic and will be revised as new clinical data become available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations*

### **Introduction**<sup>1-4</sup>

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric and psychometric test performance abnormalities occurring in patients with significant liver dysfunction after exclusion of other known brain diseases. The goals of treatment include identification and correction of precipitating factors, as well as measures aimed at reducing the brain concentration of ammonia. Precipitating factors may include GI hemorrhage, increased protein intake, infection (including spontaneous bacterial peritonitis), prerenal azotemia, hypokalemic alkalosis, constipation, hypoxia, or the use of sedatives and tranquilizers. Reduction of ammonia load can be achieved by acidifying the contents of the colonic lumen, by cleansing the bowel, and by the use of antibiotics.

### **First-line Treatment**<sup>1</sup>

Lactulose has become the standard drug in the treatment of HE given its good safety profile and large clinical experience, even though the evidence from clinical trials is not conclusive. Lactulose is a nonabsorbable disaccharide that reduces ammonia by acidifying the colon and reducing the colonic transit time. It is only available as a solution for oral or rectal administration.

**Acute episodic HE:** Lactulose should be given initially at a large dose (40-50mL) every 1 to 2 hours until a bowel movement occurs. After catharsis begins, the oral dose should be adjusted to obtain two to three soft bowel movements/day (usually 15 – 30mL twice daily). Alternatively, lactulose enemas (300mL in one liter of water) should be given every 6 to 8 hours until the patient is able to tolerate oral intake. Short-term (<72 hours) protein restriction may be considered in severe HE.

**Chronic or persistent HE:** Lactulose is typically started at dosages of 15-30mL orally twice daily with dosage adjustments to obtain 2 to 3 soft bowel movements per day. Initial loading dose is not necessary for chronic or persistent HE. Long-term protein restriction is not recommended; suggested protein intake in cirrhotics (with or without HE) is 1 – 1.5g/kg/day. Protein from dairy or vegetable sources may be preferable to animal protein.

#### **Side effects:**

The common side effects of lactulose therapy include unpleasant taste, bloating, abdominal cramps, and diarrhea. Care should be taken to avoid diarrhea; resulting dehydration and electrolyte abnormalities can worsen HE and lead to renal dysfunction. If diarrhea develops, lactulose should be withheld until diarrhea resolves and then restarted at a lower dose.

### **Second-line Treatment**<sup>1,5-7</sup>

Rifaximin, non-absorbed rifamycin antibiotic, is a second-line alternative to lactulose for the treatment of HE. Rifaximin should be reserved for patients with HE that is non-responsive to lactulose or in patients intolerant to lactulose. Rifaximin has orphan drug designation for use in HE and is currently undergoing Phase III clinical trials. Similar to other antibiotics, rifaximin achieves reduction of ammonia load by elimination of colonic bacteria.

#### **Patient Selection for Use of Rifaximin for Treatment of HE:**

- 1) *Refractory to lactulose:* Patient continues to experience HE symptoms despite receiving lactulose at a dose that obtains 2 – 3 loose stools per day. Both endpoints (HE symptoms and number of loose stools per day) should be documented in patient's medical record.
- 2) *Intolerance to lactulose:* Patient with  $\geq 4$  loose stools per day despite dosage reductions. Both endpoints (number of loose stools per day and dosage adjustments) should be documented in the patient's medical record.

**Dosage for Acute episodic HE & Chronic or persistent HE:** Rifaximin 400mg orally three times daily with or without food. The manufacturer does not provide recommendations for use in patients unable to swallow; however, it appears that the 200mg tablets may be crushed. In Phase III clinical trials, rifaximin 550mg orally twice daily is being evaluated for treatment of HE. The 550mg tablet of rifaximin is currently not available in the United States.

**Side effects:**

Rifaximin is generally well-tolerated. Diarrhea and abdominal pain have been reported. In postmarketing experience, rare hypersensitivity reactions including exfoliative dermatitis, angioneurotic edema, and urticaria have been reported.

**Monitoring and Evaluation**

- 1) After evaluating for initial response and tolerability, reassess medical treatment for HE every 3 months to confirm on-going need of rifaximin therapy. In addition to assessing the clinical signs and symptoms of HE, it is important to monitor the hydration status and electrolytes of the patient.
- 2) In patients who have not achieved optimal control of HE with rifaximin monotherapy, consider combination of rifaximin and lactulose therapy.

**Alternative Therapies<sup>1</sup>**

Neomycin or metronidazole can be utilized as alternative agents in the treatment of HE. However, toxicities have limited the clinical utility of these agents. Neomycin, a poorly absorbed aminoglycoside, may cause nephrotoxicity and ototoxicity while long-term therapy with metronidazole has been associated with peripheral neuropathy.

**Table 1. Costs of Agents for the Management of Hepatic Encephalopathy**

Drug	Dosage	Cost Per Unit	Cost Per Day
Rifaximin	400mg (2x200mg) orally three times daily	\$2.09 / 200mg	\$12.54
Lactulose Solution (20gm/30mL)	15 – 30mL orally three times daily*	\$0.08-\$0.16 / 15-30mL	\$0.24-\$0.48
Neomycin	1gm (2x500mg) orally three times daily	\$0.28 / 500mg	\$1.68

\*Dose of lactulose is adjusted to maintain 2-3 loose stools per day.

**References**

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