CDEC FINAL RECOMMENDATION

RIFAXIMIN
(Zaxine — Salix Pharmaceuticals Inc.)
Indication: Overt Hepatic Encephalopathy

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that rifaximin be listed for reducing the risk of overt hepatic encephalopathy (HE) recurrence, if the following clinical criteria are met:

Clinical Criteria:
- Patients are unable to achieve adequate control of HE recurrence with lactulose alone.
- Used in combination with a maximal tolerated dose of lactulose.

Reasons for the Recommendation:
1. One double-blind, phase 3, randomized controlled trial (RCT) (study 3001; N = 299), in which 91% of participants were using concomitant lactulose therapy, demonstrated that treatment with rifaximin significantly reduced the risk of breakthrough overt HE (hazard ratio [HR] 0.421; 95% confidence interval [CI], 0.276 to 0.641]) and HE-related hospitalization (HR 0.500; 95% CI, 0.287 to 0.873) compared with placebo.
2. At the submitted price ($15.36 per day), the CADTH Common Drug Review (CDR) estimated that the incremental cost-utility ratio (ICUR) for rifaximin plus lactulose versus lactulose alone ranges from being dominant to $22,571 per quality adjusted life-year (QALY).

Background:
Rifaximin is an orally administered broad-spectrum antibiotic belonging to the rifamycin class and is indicated for reducing the risk of overt HE recurrence in patients who are at least 18 years of age. Rifaximin is available as 550 mg tablets and the recommended dose is one 550 mg tablet taken orally twice daily, without food.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of rifaximin, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with overt HE.

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Patient Input Information

The following is a summary of information provided by four patient groups that responded to the CDR call for patient input:

- Symptoms of HE, even when not overt, have a significant negative impact on an individual's quality of life and their physical and cognitive functioning. In particular, HE weakens memory, interferes with sleep, slows thinking, and increases aggression. Patient groups indicated that HE often results in repeated and prolonged hospitalizations.
- Patients with overt HE are often unable to perform child care or other caregiver duties and are often unable to work, thereby making them financially dependent upon caregivers and/or social assistance. This places an emotional and financial burden on other family members who need to care for those affected by HE.
- Patient groups noted that lactulose is currently the first-line treatment for overt HE, but that it is limited by significant side effects, including gas, bloating, abdominal pain, flatulence, and diarrhea. Patients indicated that not all patients respond to lactulose and that compliance can be a problem, due to poor palatability and the need for frequent dosage adjustments.

Clinical Trials

The CDR systematic review included two double-blind RCTs that compared rifaximin 550 mg twice daily with placebo. Study 3001 (N = 299) was a manufacturer-sponsored, multinational phase 3 pivotal trial that enrolled patients who had at least two episodes of overt HE within six months of randomization, and were in remission from HE at baseline. Patients were randomized (1:1) to either rifaximin or placebo over a six-month treatment course. Most patients (91%) used lactulose at baseline and continued to use lactulose throughout the study. The other study, Ali et al. (N = 126), was a published, single-centre, investigator-initiated study conducted in Pakistan; the methods and results were not well reported, and generalizability to Canadian clinical practice was uncertain. Hence, the CDR review and CDEC's deliberations focused on study 3001.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Time to first breakthrough episode of overt HE — defined by changes in two symptom scoring instruments used in HE: an increase in Conn score (a five-point scale that assesses neurocognitive function) to grade ≥ 2, or an increase of one grade in both Conn and asterixis scores (a five-point scale that assesses asterixis [i.e., flapping tremor]) in patients with a Conn score of 0 at baseline
- Time to HE-related hospitalization
- Time to increase in Conn score
- Time to increase in asterixis grade
- Change from baseline in the fatigue domain of the Chronic Liver Disease Questionnaire (CLDQ) — a disease-specific health-related quality of life instrument used to measure longitudinal change over time in patients with chronic liver disease.

The primary outcome in study 3001 was time to first breakthrough episode of overt HE.

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Efficacy

- Rifaximin was statistically significantly superior to placebo for time to first breakthrough episode of overt HE, with an HR of 0.421 (95% CI, 0.276 to 0.641); *P* < 0.0001.
- Subgroup analyses demonstrated similar results for patients with (HR 0.248 [95% CI, 0.108 to 0.571]) and without (HR 0.512 [95% CI, 0.313 to 0.839]) significant comorbidities that may increase the risk of developing overt HE.
- Rifaximin was statistically superior to placebo for hospitalizations related to HE, with an HR of 0.500 (95% CI, 0.287 to 0.873) (*P* = 0.0129). Data regarding the duration of hospitalizations and all-cause hospitalizations were not reported.
- There were fewer events of worsened Conn scores in the rifaximin group (n = 37) compared with the placebo group (n = 77), with an HR of 0.463 (95% CI, 0.312 to 0.685); *P* < 0.0001.
- There were numerically fewer events of worsened asterixis scores in the rifaximin group (n = 32) compared with the placebo group (n = 50); however, the difference was not statistically significant (HR 0.646 [95% CI, 0.414 to 1.008]; *P* = 0.0523).
- There were no statistically significant differences between rifaximin and placebo for changes in any of the CLDQ domain scores according to the pre-specified analysis plan for this outcome.

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was 80% in both the rifaximin and placebo groups. The most commonly reported adverse event was HE (12% with rifaximin and 21% with placebo). Other common adverse events with a greater than 5% difference between the rifaximin and placebo groups were peripheral edema (15% versus 8%, respectively) and dizziness (13% versus 8%, respectively).
- Serious adverse events were reported in 36% of rifaximin-treated patients and 40% of placebo-treated patients. The most commonly reported serious adverse events (rifaximin versus placebo, respectively) were anemia (3% versus 0), ascites (3% in each), esophageal varices (3% versus 1%), hepatic cirrhosis (2% versus 4%), pneumonia (3% versus 1%), and acute renal failure (1% versus 3%).
- Withdrawals due to adverse events were reported for 21% of rifaximin-treated patients and 28% of placebo-treated patients. HE was the most commonly reported adverse event leading to withdrawal from the study (10% versus 19% with rifaximin and placebo, respectively).

Cost and Cost-Effectiveness

The manufacturer submitted a reduced price during the embargo period of $7.6775 per 550 mg tablet ($15.36 daily). This represents a 34% price reduction from the originally submitted price of $11.6400 per tablet ($23.28 daily).

The manufacturer submitted a cost-utility analysis comparing rifaximin + lactulose, assumed to be used in 91% of patients, with lactulose over a 10-year time horizon in patients with chronic liver disease and an average of 2.5 HE episodes within six months. Patients could remain free of HE, or develop an HE episode with a transient decrease in quality of life, and risk of hospitalization for HE (with attendant costs). The risks of HE episode and related hospitalization were obtained from study 3001. It was assumed that there was a 30% reduction in length of stay (and costs) for HE hospitalizations in patients receiving rifaximin + lactulose compared with lactulose alone. Mortality for rifaximin + lactulose was obtained from the extension study 3002

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(0.15/person-exposure-year), while mortality for lactulose alone was obtained from the placebo group of study 3001 (0.24/person-exposure-year).

A key limitation of the submitted economic model is the assumption of survival benefit with rifaximin + lactulose compared with lactulose alone as there is no clinical trial data to support this assumption. This assumption is the main driver of the health benefit for rifaximin + lactulose. A second key assumption, not substantiated by study 3001, is that length of stay for HE episodes requiring hospitalization is 30% shorter for patients receiving rifaximin + lactulose versus lactulose alone.

Based on the reduced price, when more conservative estimates of mortality rate and hospital length of stay for HE are applied, the ICUR for rifaximin + lactulose versus lactulose alone ranged from being dominant to $22,571 per QALY.

At the recommended dose of 550 mg twice daily, based on the reduced price, the annual cost of rifaximin is $5,605.

Other Discussion Points:
CDEC noted the following:
- The clinical expert consulted during the review indicated that absolute intolerance to lactulose is not commonly encountered in clinical practice.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:
- Of patients in study 3001, 91% were being treated with concomitant lactulose; therefore, the clinical benefit of treating overt HE with rifaximin as monotherapy is uncertain.
- Potential antimicrobial resistance with long-term use of rifaximin in patients with overt HE requires further evaluation.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

Regrets:

January 21, 2015: None
March 18, 2015: One CDEC member was unable to attend the meeting.

Conflicts of Interest:

January 21, 2015: None
March 18, 2015: None

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About This Document:

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The manufacturer has reviewed this document and has not requested the removal of confidential information.

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