Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	rifaximin (Zaxine) (550 mg tablet)
Indication	For the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Listing request	For patients who are unable to achieve adequate disease control; i.e., controlling HE recurrence, with lactulose alone, or for patients who are at risk of recurrent HE who are unable to tolerate lactulose.
Manufacturer	Salix Pharmaceuticals Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in the treatment of liver disease who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CIHI	Canadian Institute for Health Information
CUA	cost-utility analysis
DB	double-blind
HE	hepatic encephalopathy
ICUR	incremental cost-utility ratio
ITT	intention-to-treat (population)
LOS	length of stay
MELD	Model for End-Stage Liver Disease
PE	pharmacoeconomic
PYE	person-year of exposure
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
SOC	standard of care
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Rifaximin (Zaxine)
Study Question	"What is the incremental cost-utility ratio (ICUR) associated with the use of rifaximin 550 mg twice daily in adult patients at risk of recurrence of hepatic encephalopathy (HE), from the perspective of a Canadian health ministry, compared with the current standard of care?"
Type of Economic Evaluation	CUA
Target Population	Adults with chronic liver disease and previous overt HE events (based on Study 3001; MELD score < 25, 2.5 overt HE events within the 6 months prior to entry).
Treatment	Rifaximin 550 mg twice daily in addition to SOC
Outcome	QALYs
Comparator	SOC (lactulose approximately 50 mL per day in 91% of patients, as per Study 3001; the remaining 9% do not receive active treatment)
Perspective	Health care payer
Time Horizon	10 years
Results for Base Case	Based on the reduced price, compared with lactulose, treatment with rifaximin is associated with an incremental 0.86 QALY, and an incremental cost of $4,627, with an ICUR of $5,394 per QALY.
Key Limitations	CDR noted a number of limitations with the manufacturer's model: • The assumed mortality benefit of rifaximin drives the majority of the QALY gains in the model; however, mortality benefit was not established by RCT data. • In addition to a reduction in overt HE events and HE hospitalizations, the model assumed that HE hospitalization LOS in rifaximin-treated patients would be 30% shorter than for patients treated with lactulose; no data from Study 3001 support this assumption.
CDR Estimate(s)	CDR performed a number of reanalyses to assess the impact of the parameters for which there is uncertainty: • Assuming equal baseline mortality for both treatment strategies reduces the QALY gain with rifaximin plus lactulose from 0.86 to 0.03, but results in cost savings ranging from $7,331 to $9,679, depending on mortality rate used: rifaximin plus lactulose dominates lactulose alone (higher drug costs with rifaximin plus lactulose are offset by lower risk of hospitalization). • Assuming equal duration of HE hospitalization for each treatment strategy increases the ICUR to $15,878. If LOS and cost of HE hospitalization are reduced by 50%, this further increases the ICUR to $22,571 per QALY. • A lower baseline probability of overt HE events than that assumed in the base case (from 2.463 to 0.5 events per 6 months) increases the ICUR to $22,042 per QALY.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; HE = hepatic encephalopathy; ICUR = incremental cost-utility ratio; LOS = length of stay; MELD = Model for End-Stage Liver Disease; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SOC = standard of care.

EXECUTIVE SUMMARY

Background

Rifaximin (Zaxine) is being reviewed for the reduction in risk of overt hepatic encephalopathy (HE) in adult patients with chronic liver disease; the requested listing criteria are for patients who are unable to achieve adequate disease control with lactulose (or who are intolerant of lactulose). Rifaximin is a poorly absorbed, semi-synthetic antibiotic with activity focused in the gastrointestinal tract. The recommended dose is 550 mg twice daily.

The manufacturer submitted a reduced price during the CADTH Common Drug Review (CDR) embargo period of $7.6775 per 550 mg tablet. This represents a 34% price reduction from the originally submitted price of $11.6400 per tablet.

The manufacturer submitted a cost-utility analysis comparing the standard of care (lactulose, assumed to be used in 91% of patients) with rifaximin plus lactulose, during 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 reduction in HE events was obtained from the Study 3001[1] hazard ratio. Baseline mortality was obtained by applying the observed mortality rate in the randomized controlled trial (RCT) to the lactulose group and the rate observed in a 24-month, open-label extension trial (Study 3002)[2] to the rifaximin plus lactulose group.

Summary of Identified Limitations and Key Results

A key limitation of the submitted economic model is the assumption of mortality benefit with rifaximin plus lactulose compared with lactulose alone, as there are no RCT data to support this assumption. The assumption of survival benefit is the main driver of the health benefit for rifaximin plus lactulose. A second key assumption, not substantiated by Study 3001, is that length of stay (LOS) for HE episodes requiring hospitalization is 30% shorter for patients in the rifaximin plus lactulose group versus the lactulose group.

CDR reanalysis based on reduced price and assuming equal mortality rate results in rifaximin plus lactulose being dominant (lower costs, more quality-adjusted life-years [QALYs]) compared with lactulose alone. There is instability of the incremental cost-utility ratio (ICUR) due to the very small incremental QALY differences (0.03 QALY or additional 11 days of perfect health over 10 years).

CDR reanalysis assuming equal hospital LOS leads to ICURs ranging from $15,878 to $22,571 per QALY for rifaximin plus lactulose versus lactulose alone.

Conclusions

Based on the reduced price, the manufacturer-submitted reference case suggests that the use of rifaximin plus lactulose versus lactulose alone results in an ICUR of $5,394 per QALY. The manufacturer's reference model assumes a mortality benefit and reduced hospital LOS for an HE event with rifaximin, which have not been established by RCT data. When more conservative estimates of mortality rate and hospital LOS for HE are applied, the ICUR for rifaximin plus lactulose versus lactulose alone ranged from being dominant to $22,571 per QALY.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer conducted a cost-utility analysis (CUA) in a patient population with chronic liver disease and overt hepatic encephalopathy (HE) episodes, based on trial participants in Study 3001[1] (inclusion criteria included at least two overt HE events in the preceding six months and a Model for End-Stage Liver Disease [MELD] score < 25).[3] The standard of care (SOC), comprising treatment with lactulose, was compared with rifaximin plus SOC. Lactulose was assumed to be used in approximately 91% of patients in both groups, consistent with Study 3001.[1] Patients could remain in remission from HE, or could develop an episode of overt HE. This event results in a transient decrease in quality of life (for 11 days), and a proportion of patients are hospitalized. The baseline risk of an HE event was derived from the frequency of HE events in the preceding six months for Study 3001 participants (2.5 events per six months). The probability of requiring hospitalization for an HE event was calculated from the pooled probability of the two groups in the trial. The hazard ratio (HR) of developing an HE event was also taken from the randomized controlled trial (RCT); as the HR and 95% confidence intervals for the primary outcome of breakthrough HE were similar to the HR of HE-caused hospitalization and HE-related hospitalization, a single HR (primary outcome) was applied. It was assumed that the probability of an HE event and the HR would continue over the patient's lifetime.

The mortality rate for rifaximin plus lactulose was obtained from the rifaximin plus lactulose group in Study 3001 (six months) and Study 3002[2] (24 months; an extension of Study 3001 that also allowed new subjects) at 0.15 per person-year of exposure (PYE). The mortality rate from the lactulose group was obtained from the lactulose group of the six-month RCT, and was 0.24/PYE. The mortality rate was doubled during an HE episode that lasted one month. Quality of life (QoL) (utility) scores were sourced from a study in which utility was obtained from both patients and physicians for the health states of decompensated cirrhosis (remission) and encephalopathy (HE event), using a time trade-off analysis.[4] The HE event disutility was assumed to last for 11 days. Drug costs were obtained from the manufacturer (rifaximin) and the Régie de l'assurance maladie du Québec (RAMQ; lactulose), and drug use was based on the RCT (100% compliance for rifaximin 550 mg twice daily; approximately 50 mL lactulose daily in approximately 91% of patients in both groups). Hospitalization costs were obtained by examining the costs by relevant Case Mix code from Canadian Institute for Health Information (CIHI) data. It was assumed that there was a 30% reduction in length of stay (LOS) (and costs) for HE hospitalizations in patients receiving rifaximin plus lactulose. As adverse events (AEs) were generally mild or moderate and serious adverse events (SAEs) were similar between the two groups, they were not included in the model. A 10-year time horizon and health care payer perspective was used.

Manufacturer's Base Case

The manufacturer's base case reported that the use of rifaximin plus lactulose resulted in an additional 0.86 QALY and an additional $4,627 in costs, with an incremental cost-utility ratio (ICUR) of $5,394 (Table 2). Disaggregated costs were not reported.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (WITH REDUCED PRICE)

	Total Costs ($)	Incremental Cost of Rifaximin plus Lactulose ($)	Total QALYs	Incremental QALYs of Rifaximin plus Lactulose	Incremental Cost ($) per QALY
Lactulose	43,834	Reference	2.45	Reference	Reference
Rifaximin plus lactulose	48,461	4,627	3.31	0.86	5,394

QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analyses: The manufacturer was not requested to provide sensitivity analysis using the reduced price and only CDR reanalyses will be presented in this revised report.

Limitations of Manufacturer's Submission

Assumption of mortality benefit: The six-month Study 3001 showed no difference in mortality between the two groups, with an identical percentage of deaths (7%) in each group.[1] The manufacturer used the mortality rate from the placebo plus lactulose group of this trial to inform the lactulose group in the model at 0.24/PYE. The mortality rate for the rifaximin plus lactulose group is obtained from this RCT and the extension study[2] (24 months, including trial participants from treatment and placebo groups [n = 152] and new patients [n = 170], with a rate of 0.15/PYE). This difference in mortality rate is a major driver of clinical benefit in the model, but it is not supported by RCT findings. While the occurrence and frequency of HE events are associated with increased mortality, it has not been established that reducing HE events alters mortality. HE has not been validated as a surrogate for survival, and the mechanism of action of rifaximin does not support that it modifies the overall course and progression of chronic liver disease. This assumption favours rifaximin.

Assumption of different length of stay and hospitalization cost by treatment: The model assumes that hospitalizations associated with HE events are 30% shorter and less costly for rifaximin plus lactulose compared with lactulose alone (7.62 days and $7,745 for lactulose alone; 5.33 days and $5,422 for rifaximin plus lactulose). The manufacturer states this is from a published meta-analysis,[5] but does not describe this meta-analysis nor uses any other data from it (this meta-analysis includes placebo-controlled treatment comparisons and open-label trials). Further, there are no data from Study 3001 that are used to defend this assumption. This assumption favours rifaximin.

Duration and cost of hospitalization for hepatic encephalopathy: There is uncertainty regarding the cost of HE hospitalization, as the Case Mix CIHI code used is broad (cirrhosis/alcoholic hepatitis). A recent RCT of polyethylene glycol (PEG) versus lactulose for hospitalized HE (Rahimi[6]) reported a similar LOS for the control group (eight days versus 7.62 days in model), although PEG reduced LOS to four days (0.07). It may be plausible that treatment of an acute HE episode, which requires hospitalization, will require a shorter LOS as the standard treatment evolves over time. As rifaximin plus lactulose is associated with less frequent HE hospitalization compared with lactulose treatment alone, an overall shorter LOS would result in smaller cost savings.

Generalizability: The study population was based on study participants in Study 3001, in which inclusion criteria mandated frequent HE events (at least two in the preceding six months) and a MELD score of < 25. While this is likely representative of a large proportion of patients, the relative and absolute efficacy is not known in patient groups with less frequent events or more severe disease. There is uncertainty regarding the cost-effectiveness in patients with different characteristics from those included here, although this may be only minor, in the opinion of the clinical expert consulted by CDR.

Duration of benefit: While the extension trial supported continued efficacy, benefit has not been established within an RCT beyond six months. Further, relative and absolute efficacy in patients with more severe disease, such as MELD > 25, is not known. If relative or absolute benefit attenuates over time, this ICUR for rifaximin plus lactulose versus lactulose alone will increase.

CADTH Common Drug Review Analyses Using Reduced Price

CDR undertook a number of reanalyses to assess the impact of some of the limitations identified with the manufacturer's model (Table 9).

- **Equal mortality:** If the reference case mortality is changed (rifaximin plus lactulose 0.15/PYE; lactulose alone 0.24/PYE) so that mortality is equal, the incremental QALYs diminish (from 0.86) and the ICUR increases.
  a. Both 0.24/PYE = incremental QALY of 0.03 and cost savings of $7,331: rifaximin plus lactulose dominates lactulose alone.
  b. Both 0.15/PYE = incremental QALY of 0.03 and cost savings of $9,679: rifaximin plus lactulose dominates lactulose alone.
- **Equal duration (and cost) of hepatic encephalopathy hospitalization regardless of treatment group** (lactulose alone 7.62 days and cost of $7,745; relative cost for rifaximin plus lactulose = 0.7)
  a. Same duration of hospitalization for lactulose and rifaximin: incremental QALY of 0.86 and incremental cost of $13,620; ICUR $$15,878 for rifaximin plus lactulose versus lactulose alone.
  b. Reduced duration and cost of hospitalization by 30% (5.4 days/$5,422), and same duration for lactulose alone and rifaximin plus lactulose: ICUR $19,893 for rifaximin plus lactulose versus lactulose alone.
  c. Reduced duration and cost of hospitalization by 50% (3.81 days/$3,872), and same duration for lactulose alone and rifaximin plus lactulose: ICUR $22,571 for rifaximin plus lactulose versus lactulose alone.
- **Varying baseline risk of hepatic encephalopathy event** (reference case 2.463 per six months)
  a. 0.5 events per six months: ICUR $22,042 for rifaximin plus lactulose versus lactulose alone.
  b. Four events per six months: ICUR $1,547 for rifaximin plus lactulose versus lactulose alone.

Issues for Consideration

- The clinical expert consulted by CDR indicated that patients frequently complain of the bad taste, nausea, and diarrhea associated with lactulose.
- Rifaximin may be used in a broader chronic liver disease population than was considered in the model.

Patient Input: Input was received from four organizations or patient groups: the Canadian Liver Foundation (CLF), the GI (Gastrointestinal) Society, Hepatitis C Education and Prevention Society (HepCBC), and the Consumer Advocare Network (Advocare). In these inputs, patients noted that HE symptoms have a significant impact on their quality of life and on their ability to function daily. Patients stated that HE attacks often result in repeated and prolonged hospitalizations. All submitting groups noted that lactulose is currently the first-line treatment for HE, but it causes significant side effects, including gas, bloating, abdominal pain, flatulence, and diarrhea. Due to necessary dosage adjustments, compliance can be a problem, leading to recurring episodes of HE when patients do not take their medication properly. In addition, not all patients respond to lactulose. Patient groups considered rifaximin to be more cost-effective as patients spend less time in hospital.

As noted in the Limitations of Manufacturer's Submission section, there are no RCT data to support the assertion that rifaximin reduces the LOS in hospital for HE episodes compared with lactulose, and this assumption may underestimate the ICUR of rifaximin compared with lactulose.

Conclusions

Based on the reduced price, the manufacturer-submitted reference case suggests that the use of rifaximin plus lactulose versus lactulose alone results in an ICUR of $5,394 per QALY. The manufacturer's reference model assumes a mortality benefit and reduced hospital LOS for an HE event with rifaximin, which have not been established by RCT data. When more conservative estimates of mortality rate and hospital LOS for HE are applied, the ICUR for rifaximin plus lactulose versus lactulose alone ranged from being dominant to $22,571 per QALY.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturers' list prices, unless otherwise specified.

TABLE 3: COST COMPARISON TABLE FOR ZAXINE

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost ($)	Annual Cost ($)
Rifaximin (Zaxine)	**550 mg**	**Tablet**	**7.6775**[a]	**550 mg twice daily**	**15.36**	**5,605**
Lactulose (generic)	667 mg/mL	Oral liquid	0.0145	30 mL to 45 mL three to four times daily, titrated to produce two to three soft stools per day[b]	1.31 to 2.61	478.15 to 953

[a] Manufacturer's revised price during embargo period. Original submitted price was $11.6400 per tablet.
[b] Dosing is from eTherapeutics Hepatic Encephalopathy entry, retrieved Sept 23, 2014.[7]
Source: Ontario Drug Benefit Formulary list prices (February 2015) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RIFAXIMIN RELATIVE TO LACTULOSE?

Rifaximin Plus Lactulose Versus Lactulose Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$5,394 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
Note: Based on manufacturer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*			
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 6: AUTHOR INFORMATION

Authors	Affiliations
Ferg Mills Eric Siu Anne-Claire Poinas George Wyatt	Wyatt Health Management

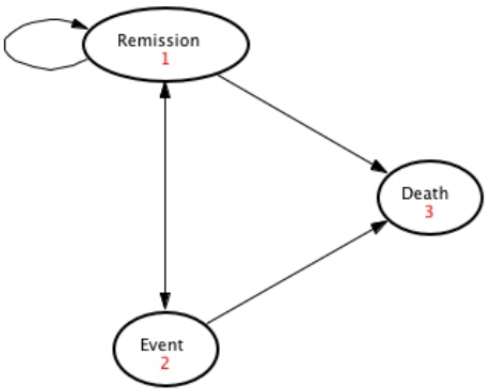
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The submitted economic model considers a population of adult patients with chronic liver disease who have had at least two episodes of overt hepatic encephalopathy (HE) in the previous six months but who are currently in remission, with a Model for End-Stage Liver Disease (MELD) score of < 25 (from Study 3001 participants). A Markov model is used to track the cohort over a 10-year time horizon, using a one-month cycle length. Patients in the model start in the health state of chronic liver disease without HE (remission) and may transition to the health state of an overt HE episode (event). After the HE episode (one cycle), the surviving patients transition back to remission. Patients may transition to the absorbing "Death" state from either "Remission" or "Event."

FIGURE 1: MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[3]

Captured within each health state are quality of life (QoL) and costs. A proportion of patients who enter into the HE event state are hospitalized, with attendant costs.

Validation was determined by assessing technical accuracy (first order validation). Comparison of model outputs with clinical data (internal or external sources) or with clinical experts (face validity) was not specifically reported.

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Study 3001 using primary outcome (HR of breakthrough HE 0.42; 95% CI, 0.28 to 0.64). As this did not differ from the HR of HE-caused hospitalizations (0.44; 95% CI, 0.24 to 0.81) or the HR of HE-related hospitalizations (0.50; 95% CI, 0.29 to 0.87), the HR for the primary outcome was assumed to apply to events and hospitalizations. The HR was applied over the patient's lifetime.	Appropriate. There may be some subjectivity in the determination of the HE episode as well as the decision to hospitalize. Trial was six months; extension trial suggests continued relative efficacy, but uncertain.
Natural history	Frequency of HE events based on trial participant history over the preceding six months. Proportion of HE events necessitating hospitalization from Study 3001 (weighted average of the two groups).	Trial inclusion criteria mandated ≥ 2 HE events in preceding six months.
Utilities	TTO analysis in patients and physicians for decompensated cirrhosis (remission) and encephalopathy (event); event assumed to last for 11 days.	Uncertainty in true QoL by health state.
Resource use		
AEs (indicate which specific AEs were considered in the model)	No AE included in model. Justified by manufacturer as most were mild or moderate, and SAEs were similar between the two groups.	
Mortality	Mortality rate from placebo group of Study 3001 (0.24/PYE); rifaximin from extension trial (0.15/PYE). The mortality rate doubles for patients admitted for HE, lasting one cycle.	RCT reports identical mortality between groups. Not clear that reduction in HE events will reduce mortality.
Costs		
Drug	Manufacturer reduced cost (rifaximin); 100% adherence (from RCT and extension). Lactulose cost from RAMQ; used in approximately 91% of patients (in both treatment groups) with daily dose of 47 mL and 53 mL (rifaximin and lactulose, respectively).	Drug adherence based on trial data; lactulose use (and cost) lower than typically prescribed.
Administration	NA	
AEs	Not included	
Remission health state	Remission health state comprised drug costs and outpatient visit every three months.	
Event health state	Outpatient consultation and drug costs. Proportion of patients hospitalized (weighted average of two groups from trial). Hospitalization cost based on CIHI-reported cost for Case Mix code cirrhosis/alcoholic hepatitis ($7,745 and 7.72 days); 30% reduction in LOS assumed for rifaximin-treated patients ($5,421).	The manufacturer refers to meta-analysis[5] indicating difference in LOS. The meta-analysis was not reported in detail, and a different LOS is not supported by Study 3001.

AE = adverse event; CI = confidence interval; CIHI = Canadian Institute for Health Information; HE = hepatic encephalopathy; HR = hazard ratio; LOS = length of stay; NA = not applicable; PYE = person-year of exposure; QoL = quality of life; RAMQ = Régie de l'assurance maladie du Québec; RCT = randomized controlled trial; SAE = serious adverse event; TTO = time trade-off.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Patient population similar to indication population	Trial selection mandated ≥ 2 HE events in the six months prior to enrolment; baseline event rate will influence absolute differences in efficacy. Also mandated MELD < 25; relative efficacy at more severe MELD scores is unclear.
Rifaximin decreases risk of HE event, HE hospitalization, and LOS for a HE-related hospitalization	RCT data support reduction in frequency of HE events and hospitalization. However, it is unclear whether a given HE hospitalization will also have a reduced LOS.
Rifaximin confers mortality benefit	Not supported by Study 3001
Hospitalization cost for HE can be informed by CIHI costs	Unclear. The Case Mix code used is broad (cirrhosis/alcoholic hepatitis) and may include a large number of reasons for hospitalization. Further, index hospitalization costs may be large (initial diagnosis and management); however, this model is evaluating hospitalization in patients with known liver disease and HE.
HE is associated with disutility	Appropriate, but true QoL differences are uncertain.
Stable probability of HE event and HR with rifaximin over time	While the extension trial suggests continued relative efficacy (compared with placebo group in RCT), uncertainty exists. Further, the baseline risk and HR in patients with more severe disease (as disease severity worsens over time) is not known.

CIHI = Canadian Institute for Health Information; HE = hepatic encephalopathy; HR = hazard ratio; ICUR = Incremental cost-utility ratio; LOS = length of stay; MELD = Model for End-Stage Liver Disease; QoL = quality of life; RCT = randomized controlled trial.

Manufacturer's Results

The manufacturer reports that the use of rifaximin plus lactulose leads to an additional 0.86 QALY and $4,627 in costs, with an ICUR of $5,394. Absolute and incremental cost by category (e.g., drug, hospitalization) were not provided.

CADTH Common Drug Review Reanalysis Using Reduced Price

The CADTH Common Drug Review (CDR) undertook a number of reanalyses to assess the impact of some of the limitations identified with the manufacturer's model (Table 9).

TABLE 9: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES BASED ON REDUCED PRICE

	Strategy	Cost ($)	Incremental Cost (Savings) ($)	QALY	Incremental QALYs	ICUR Rifaximin vs. Lactulose ($)
Equal baseline mortality (0.15/PYE)	Lactulose	58,140.09	Ref	3.28	Ref	Ref
	Rifaximin	48,460.91	(9,679.18)	3.31	0.03	Dominant
Equal baseline mortality (0.24/PYE)	Lactulose	43,833.92	Ref	2.45	Ref	Ref
	Rifaximin	36,502.93	(7,330.98)	2.48	0.03	Dominant
Equal LOS ($7,745 per hospitalization)	Lactulose	43,834.13	Ref	2.45	Ref	Ref
	Rifaximin	57,454.34	13,620.21	3.31	0.86	15,878
Equal LOS (70% duration vs. base case, $5,422 per hospitalization)	Lactulose	31,398.95	Ref	2.45	Ref	Ref
	Rifaximin	48,462.85	17,063.9	3.31	0.86	19,893
Equal LOS (50% duration vs. base case, $3,872 per hospitalization)	Lactulose	23,101.83	Ref	2.45	Ref	Ref
	Rifaximin	42,463.46	19,361.63	3.31	0.86	22,571
Equal baseline mortality (0.24/PYE) and equal LOS ($7,745 per hospitalization)	Lactulose	43,833.92	Ref	2.45	Ref	Ref
	Rifaximin	43,293.23	(540.69)	2.48	0.03	Dominant
Baseline risk of HE event reduced to 0.5 per 6 months	Lactulose	14,285.67	Ref	2.47	Ref	Ref
	Rifaximin	32,501.34	18,215.67	3.30	0.83	22,042
Baseline risk of HE event increased to 4 per 6 months	Lactulose	56,259.26	Ref	2.44	Ref	Ref
	Rifaximin	57,609.04	1,349.78	3.31	0.87	1,547

HE = hepatic encephalopathy; ICUR = incremental cost-utility ratio; LOS = length of stay; PYE = person-year of exposure; QALY = quality-adjusted life-year; Ref = reference; SA = sensitivity analysis; vs. = versus.

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