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Cost-Effectiveness of Rifaximin Treatment in Patients with Hepatic Encephalopathy

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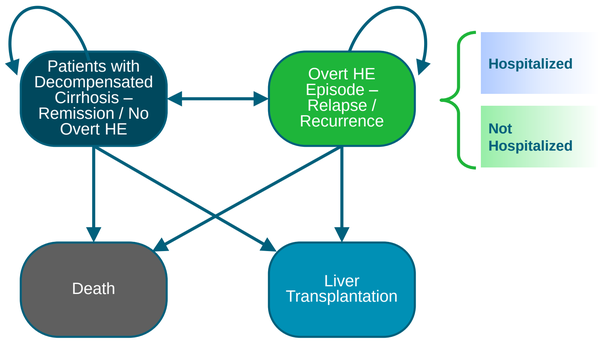
PREMISE

- After an initial episode of overt hepatic encephalopathy (HE), secondary prophylactic therapy is usually recommended for an indefinite period of time[1]
- Lactulose is frequently recommended for maintenance of remission from HE despite the lack of randomized, placebo-controlled studies to support its use[1-3]
- The poor tolerability and need for frequent titration may limit the utility of lactulose as a maintenance medication
- Rifaximin (XIFAXAN® 550 mg tablets), a minimally absorbed oral antimicrobial agent, was approved for reduction in risk of overt HE recurrence by the FDA in 2010. Over a 6-month period, rifaximin maintained remission from HE more effectively than placebo and significantly reduced the risk of HE-related hospitalizations[4]
- The protection from HE remission and HE-related hospitalization was preserved in a ≥24-month, open-label follow-up study[5]
- Results from a recent randomized controlled trial suggest that, among patients hospitalized for overt HE, the use of rifaximin leads to a greater percentage of patients with complete reversal of HE and a decrease in mortality compared to lactulose alone[6]
- The current study aimed to assess whether these clinical benefits would be observed at a reasonable cost to a third-party payer in the US. For this purpose, a cost-effectiveness model was developed for patients who are in remission from recurrent HE resulting from chronic liver disease

METHODS

- An Excel-based cost-effectiveness model was created to predict outcomes and costs of patients with HE after initiation of maintenance therapy with lactulose alone or lactulose plus rifaximin 550 mg BID (twice a day) to avoid recurrent HE episodes
- Model Structure and Assumptions (Figure 1)
  - The cohort of patients is assumed to begin in the Remission state and is at risk for an overt HE episode, death, or liver transplantation in each 2-week cycle
  - The risk of non-HE-related hospitalizations is assumed to apply to the group of patients in remission
  - Patients in the Overt HE state (with or without a hospitalization) can transition back to the Remission state, die, or receive a liver transplant
  - Patients transitioning to the Death state exit the model after accruing appropriate costs and outcomes
  - The Liver Transplantation state is also an absorbing, or exit, state
  - Patients accrue the cost of transplantation and the average life expectancy post-transplantation is applied in life years (LYs) and quality adjusted life years (QALYs)

Figure 1 Model Structure



Analyses

- Clinical outcomes
  - Hospitalizations per patient (all-cause, HE-related, and non-HE-related)
  - Number of liver transplantations (per 100 patients)
  - Discounted and undiscounted LYs and QALYs per patient
- Total costs associated with each treatment were reported in aggregate and by component (drug, hospitalization, and liver transplantation)
- Cost-effectiveness of rifaximin was assessed through estimation of the incremental costs per LY gained, per QALY gained, and per hospitalization avoided

ANALYSES

- The impact of model parameters on outcomes was evaluated via one-way and probabilistic sensitivity analysis (PSA)
- The analysis was run separately over a 6-month time horizon, consistent with the duration of the pivotal, randomized, controlled trial and over a lifetime horizon to project the potential impact on LYs and QALYs
- Analyses were conducted from the perspective of a third-party payer in the US

MODEL INPUTS

Table 1. Clinical Model Inputs

Input	Rifaximin ± Lactulose	Placebo ± Lactulose
Population		
% on concomitant lactulose[4]	91.4%	91.2%
Overt State		
% hospitalized among those with an overt episode [4]	61.5%	49.2%
% reversed after 2 weeks among hospitalized patients[6]	76%	44%
In-hospital 2-week mortality[6]	23.8%	49.1%
Two-week mortality after hospitalization[5]	0.6%	0.9%
Non-hospitalized 2-week mortality[5]	0.6%	0.9%
Health utility for HE[7]	0.55[c]	
Remission State		
% with overt episodes by 6 months[4]	22.1%	45.9%
Hospitalizations per PYE[5]	0.24[a]	0.58[b]
Mortality at year 5[5]	52.8%	69.9%
Health utility[7]	0.74[d]	
Liver Transplantation		
Number of liver transplantations per patient per year[5]	0.061	0.061
Life expectancy after liver transplantation[8]	18.3 years	
Health utility after liver transplantation[7,9]	0.78	
Costs[e] (US$)		
Cost per HE-related hospitalization[11-13]	13,691	17,038
Cost per non-HE-related hospitalization[12,14]	10,515	
Cost per liver transplantation[12,15]	130,162	

[a]Based on all rifaximin group. [b]Based on historical placebo group. [c]Based on patient reported utility for encephalopathy. [d]Patient-reported health utility for decompensated cirrhosis.[e]Drug costs per day for rifaximin and lactulose were $44.05[10] and $1.28[10], respectively. PYE – person-years of exposure

RESULTS

Table 2. Survival and Liver Transplantations Predicted Over a Lifetime for Patients with HE

Outcome	Rifaximin + Lactulose	Placebo + Lactulose	Difference
Discounted			
LYs per patient	5.7	2.8	2.9
QALYs per patient	4.3	2.1	2.2
Undiscounted			
LYs per patient	7.1	3.3	3.9
QALYs per patient	5.4	2.5	2.9
Number of liver transplantations (per 100)	20	9	11

RESULTS

Table 3. Hospitalizations Prior to Liver Transplantation by Cause and Time Horizon

Type of Hospitalization	Hospitalizations per patient (prior to liver transplant): Rifaximin + Lactulose	Placebo + Lactulose	Difference*
Time Horizon: 6 Months			
HE-related	0.16	0.27	-0.11
Non-HE-related	0.11	0.24	-0.13
All	0.27	0.51	-0.24
Time Horizon: Lifetime			
HE-related	1.27	1.12	0.14
Non-HE-related	0.80	0.86	-0.06
All	2.06	1.98	0.08

Key: HE – hepatic encephalopathy; LY – life-year; QALY – quality-adjusted life-year.
*Calculated difference may not be equal to the difference reported in the table due to rounding.

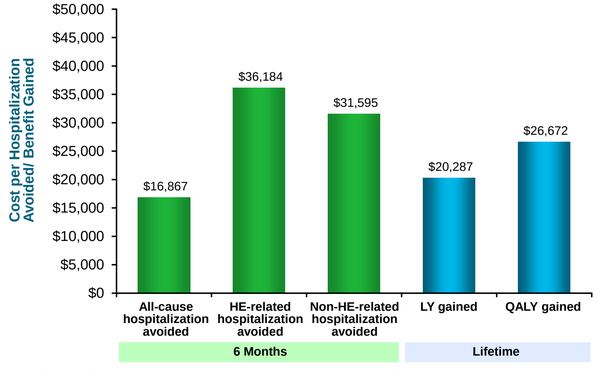
- **Rates of hospitalization**
  - Hospitalization rates were lower over 6 months (0.27 vs 0.51 per patient) and marginally higher over a lifetime (2.06 vs 1.98 per patient) with rifaximin owing to added life expectancy[4]

Table 4. Economic Results at 6 Months and Lifetime

	6 Month Time Horizon: RFX + LAC	PBO + LAC	Difference	Lifetime Time Horizon: RFX + LAC	PBO + LAC	Difference
Drug costs	$7,643	$185	$7,458	$51,400	$654	$50,746
Other direct costs	$6,858	$10,275	($3,416)	$47,319	$38,289	$9,031
Hospitalizations	$3,264	$7,006	($3,742)	$23,261	$26,880	($3,619)
HE-related	$2,123	$4,529	($2,407)	$15,607	$18,240	($2,633)
Non-HE-related	$1,142	$2,477	($1,335)	$7,654	$8,640	($987)
Liver transplantations	$3,594	$3,268	$326	$24,058	$11,408	$12,650
Total	$14,501	$10,459	$4,042	$98,719	$38,942	$59,777

Key: RFX – rifaximin; LAC – lactulose; PBO – placebo; HE – hepatic encephalopathy.

Figure 2. Incremental Cost-effectiveness Ratios

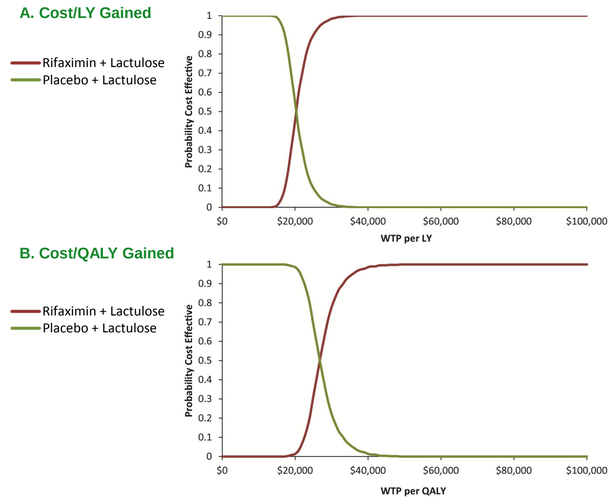


Key: HE – hepatic encephalopathy; LY – life-year; QALY – quality-adjusted life-year.

SENSITIVITY ANALYSIS

- **Costs per HE-hospitalization avoided were most sensitive to variation in the:**
  - Percentages of patients with overt HE
  - Risk of subsequent HE episodes (lactulose only patients)
  - Percent of patients suffering an overt episode who are hospitalized (lactulose only patients)
- **Incremental Cost-Effectiveness Thresholds**
  - Cost/LY: Rifaximin + lactulose is estimated to be cost-effective more than half the time when the willingness to pay (WTP) threshold is ~$20,000 or above
  - Cost/QALY: Rifaximin + lactulose is estimated to be cost-effective more than half the time when the WTP threshold is ~$25,000 or above. These estimates are well within the commonly accepted ICER threshold of $50,000 and even within the more restrictive threshold of $30,000[16]

Figure 3. Lifetime Cost-effectiveness Acceptability Curve



Key: LY – life-year; QALY – quality-adjusted life-year; WTP – willingness-to-pay.

CONCLUSIONS

- **The clinical benefits of rifaximin (e.g., reduction in risk of recurrent HE and hospitalizations), combined with an acceptable economic profile, demonstrate the potential advantages of a rifaximin maintenance regimen depending on willingness to pay thresholds of the payer and time period considered**

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