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ORIGINAL RESEARCH

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Budget impact of optimizing rifaximin-α use for the prevention of recurrent hepatic encephalopathy in The Netherlands

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ABSTRACT

Aims: Rifaximin-α as an adjunct to lactulose is reimbursed in the Netherlands for prevention of the third and subsequent episodes of overt Hepatic Encephalopathy (HE) in cirrhotic patients. However, use of rifaximin-α remains limited. This study evaluates the clinical and economic impact of treating all patients eligible under Dutch reimbursement conditions with rifaximin-α as an adjunct to lactulose for the prevention of overt HE in the Netherlands from a hospital and healthcare payer's perspective.

Materials and methods: A budget impact analysis was performed following national and international guidelines. Resource use was based on Dutch real-world data. HE-related cost inputs were based on the declaration codes, Dutch cost manual, and actual drug list prices. Several sensitivity and scenario analyses were conducted to assess model robustness.

Results: Treating eligible HE patients with rifaximin-α in addition to lactulose saves €4,487 and costs €249 per patient over a 5-year period compared with lactulose monotherapy from hospital and healthcare payer's perspectives, respectively. In the Netherlands, an estimated 38% of the 2,567 eligible patients are currently being treated with rifaximin-α. Optimizing rifaximin-α use by treating all eligible patients with the rifaximin-α + lactulose could save more than 3,000 hospital admissions, almost 15,000 hospital bed days, and 300 deaths over a 5-year period. Despite increased drug costs, treatment is estimated to result in potential cost savings over a 5-year period of 7.2 million euros from a Dutch hospital perspective. The budget impact is 397,770 euros from a healthcare payer's perspective.

Conclusions: Next to a clinical perspective, also from an economic perspective, wider prescription of rifaximin-α adhering to guidelines could be beneficial to reduce costs from a hospital perspective. From a healthcare payer's perspective, costs increase with addition of rifaximin-α due to relative better survival causing relatively higher drug and liver transplantation-related costs.

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Introduction

Hepatic encephalopathy (HE) is a severe complication of cirrhosis resulting from hepatic insufficiency and/or portosystemic shunting. In HE, the liver is unable to sufficiently clear the blood of neurotoxins, such as ammonia, which cross the blood-brain barrier, thereby resulting in physical and mental changes. HE is associated with a wide range of neurological and psychiatric symptoms, from mild confusion to coma[1]. Depending on the severity of symptoms, HE can be classified by the West Haven criteria into minimal, covert, or overt HE.

HE is associated with a high disease burden, as even mild HE impacts patients' everyday life[2]. Furthermore, HE is an independent predictor of mortality in patients with cirrhosis, with a reported inpatient mortality of 15%[1,3]. In addition to a high patient burden, HE also burdens caregivers[4]. The economic burden of HE is also significant, with mean direct costs estimated at $13,270 ($5,370–$50,120) per patient with overt HE per year globally[5]. Total costs would be even higher when considering indirect HE-related costs such as road accidents, falls, and productivity losses.

The current standard-of-care for the prevention of recurrent HE episodes in the Netherlands is lactulose[6]. Even though lactulose has been proven to be an effective treatment, adherence to long-term lactulose treatment is often suboptimal because of side effects (such as flatulence, diarrhea, abdominal pain, and nausea) and the relatively complex dosing regimen[7]. In 2016, rifaximin-α (XIFAXAN[i]) was accepted for reimbursement in the Netherlands as an adjunct to lactulose for prevention of the third and subsequent episodes of overt HE in patients aged 18 years and older[8,9]. In clinical Phase 3 trials, twice-daily 550 mg of

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rifaximin-α as add-on therapy to lactulose for the prevention of a third episode of overt HE has been shown to maintain remission more effectively, and to significantly reduce the risk of hospitalization compared to lactulose monotherapy, without increasing the risk of adverse events[10,11]. Multiple real-world studies confirm these findings by showing rifaximin-α's beneficial impact on resource use[12–15]. A real-world Dutch study in the Erasmus University Medical Center, Rotterdam, has shown that the addition of rifaximin-α to lactulose treatment was associated with a significant reduction in the number and length of overt HE-related hospitalizations[12]. Another retrospective study showed that rifaximin-α treatment was significantly associated with prolonged overall survival compared to lactulose monotherapy[13]. Therefore, the American Association for the Study of Liver Diseases/ European Association for the Study of the Liver (AASLD/ EASL) guideline recommends rifaximin-α in addition to lactulose for the prevention of recurrent episodes of HE after the second episode[1]. This is based on a UK randomized, double-blind, placebo-controlled trial which only assessed the efficacy of rifaximin-α after experiencing at least two episodes of overt HE[10]. Efficacy of rifaximin-α after one episode of HE was not explored in this study. Rifaximin-α is the best available treatment for HE in the Netherlands. Treatment with rifaximin-α and lactulose is continued until the risk of HE is taken away by liver transplantation (LT).

Despite these benefits, use of rifaximin-α remains limited in Dutch clinical practice[16]. A possible explanation for this may be the higher drug costs. Yet, the prevention of HE episodes and their related complications may also lead to possible savings for hospitals and health insurers. Multiple cost-effectiveness analyses of rifaximin-α for preventing recurrence of overt HE episodes have been published[5,17,18]. A systematic review of these cost studies concluded that economic data are favorable for use of rifaximin-α for cost-effectively reducing the risk of overt HE recurrence in patients with a history of overt HE[5]. To date, few budget impact analyses have been published on this comparison[19].

The objective of this study was to perform a budget-impact analysis to evaluate the clinical and economic impact of treating all patients who are eligible according to Dutch reimbursement conditions with rifaximin-α as an adjunct to lactulose for the prevention of the third and subsequent episodes of overt HE in the Netherlands from both hospital and healthcare payer's perspectives.

Methods

Study design

A budget impact analysis was performed and reported following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force report Budget Impact Analysis – Principles of Good Practice, designed with the use of an Excel-based cost-calculator model[20]. The budget impact model enables the calculation of the clinical and economic impact of optimizing treatment with rifaximin-α in addition to lactulose for preventing recurrence of overt HE in patients aged 18 years or older in Dutch clinical practice.

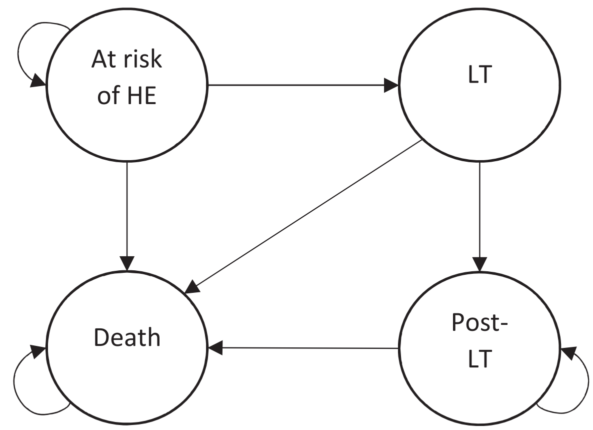

Figure 1. Schematic representation of the Markov Model. Abbreviation. LT, liver transplantation.

Total costs were estimated for the current suboptimal rifaximin-α uptake and for an optimized rifaximin-α uptake. The budget impact was defined as the total cost difference between these two scenarios. Costs associated with overt HE include hospitalizations, hospital bed days, treatment costs of lactulose and rifaximin-α, and outpatient appointments, depending on the chosen perspective of the analysis. A societal perspective has not been considered and thus indirect costs such as HE-related road accidents, falls, informal care costs and productivity losses were not included in this analysis.

Model structure

The model consists of a four-state ("At risk of HE", "dead", "LT" and "post-LT") Markov model in order to incorporate disease- and treatment-specific mortality using a static cohort based HE prevalence numbers (Figure 1). All patients enter the model in the health state "At risk of HE" that represents patients at risk of third or subsequent recurrent HE. Upon LT, patients move to the "LT" state for the duration of one cycle, after which they move to the "post-LT" state. After LT, treatment with rifaximin-α and lactulose is assumed to be discontinued. All patients in the states "At risk of HE", "LT", and "post-LT" were at risk of moving to the state "death".

A cycle length of six months was used in the model because this was in line with study data used to estimate resource use and was considered to be of sufficient granularity. Half-cycle correction was applied so patients were assumed to die halfway through a cycle rather than at the beginning or at the end. Costs were applied to patients still alive ("At risk of HE", "LT", and "Post-LT") halfway through each cycle.

Patient population

The target population of this budget impact analysis consists of patients who are eligible according to the Dutch reimbursement conditions for treatment with rifaximin-α, but who have not yet been treated. According to the Dutch reimbursement conditions, rifaximin-α is reimbursed when added to lactulose for prevention of a third or subsequent episodes of overt HE in patients aged 18 years and older[9]. To estimate the number of patients in the target population, we first multiplied the Dutch adult population (13,924,408)[21] by the prevalence of cirrhosis in the Netherlands. There are no estimations of the prevalence of cirrhosis in the Netherlands available from literature. Therefore, the prevalence of cirrhosis was based on an estimated average of 0.32% of to estimates from public registrations of diagnosis codes: (1) International Classification of Primary Care (ICPC)-code for cirrhosis/other liver disease, mentioned in the Dutch general practitioners' guideline for liver disease (0.44%)[22], and (2) International Statistical Classification of Diseases and Related Health Problems (ICD)-9 code for liver cirrhosis (0.20%)[23]. Both are used country-wide for patients visiting the general practitioner and hospital, respectively. This resulted in 44,558 patients with cirrhosis. Next, the number of patients with cirrhosis was multiplied by the risk of experiencing a first overt HE episode. As there was no point estimate available, the risk was based on an average of 15% (5–25%) of patients who have a first bout of overt HE in the first 5-years after cirrhosis diagnosis, according to the AASLD/EASL guideline[1]. However, the 5-year risk likely overestimates the point estimate of the risk of the number of patients entering the model in year 1. Therefore, the estimated risk was assumed to be 9%, calculated from the average of a yearly risk of 3% (15%/5), and a maximum of 15%. This means that we assume that 3% of patients surviving 1 year post-cirrhosis diagnosis have experienced $\geq$1 episode, 6% of patients surviving 2 years post-cirrhosis diagnosis have experienced $\geq$1 episode, etc. Subsequently, the number of patients with a first episode of overt HE was multiplied by the percentage of lactulose-treated patients who experience a second HE episode in the same year (64%)[7]. This resulted in an estimation of 2,567 patients eligible for rifaximin-α treatment. Based on the GIP databank from the National Health Care Institute, the current number of rifaximin-α users in the year 2020 was 969 patients (38%)[14]. Based on the AASLD/EASL guideline and reimbursement conditions, rifaximin-α is recommended for all patients who have previously experienced two episodes of overt HE[1]. The current estimated number of 969 rifaximin-α users represent the under treatment of eligible HE patients. The remaining 1,598 patients (62%) currently being treated with lactulose monotherapy, but who are eligible for rifaximin-α + lactulose combination therapy according to Dutch reimbursement conditions, form the estimated target population entering the budget impact model (Table 1).

Intervention and comparator

The target population could either be treated with rifaximin-α and lactulose combination therapy (intervention – referred to as rifaximin-α + lactulose) or lactulose monotherapy (comparator). The budget impact is calculated by assuming that all 1,598 patients who, according to Dutch reimbursement conditions, are eligible for rifaximin-α treatment and who are not yet being treated with rifaximin-α, will start rifaximin-α treatment when entering the model in the first year (2020). Treatment with rifaximin-α and lactulose is continued until death or liver transplantation.

Time horizon

A time horizon of 5 years was used in the model, as it was considered that the budget impact was only of interest to hospitals and national health insurers over a relatively short period. A time horizon of 5 years is in line with relevant planning horizons of Dutch policymakers, and the ISPOR Budget Impact Analysis – Principles of Good Practice[20]. Functionality within the model is designed such that results can be presented at any annual time horizon up to 5 years.

Perspectives

Two perspectives have been included in this analysis: the hospital perspective and the healthcare payer's perspective. For both perspectives, the clinical impact has been expressed in the number of hospital bed days, hospitalizations and deaths avoided. The economic impact, on the other hand has been calculated differently for each perspective, as explained below.

Rifaximin-α + lactulose combination therapy reduces the number of hospital admissions as well as bed days per hospital admission compared with lactulose monotherapy[12]. From the hospital perspective, the outcome of interest for the cost calculations was the number of inpatient bed days avoided. In the Netherlands, the hospitals receive fixed reimbursement for each hospital admission based on mean costs in the form of declaration codes (DBCs) for three categories of length of stay (1–5 days, 6–28 days, or 28+ days). Therefore, the potential for cost savings from this perspective comes from the reduction in bed days per hospital admission because this will free up capacity allowing for care of more patients. The total number of hospital bed days avoided was calculated by multiplying the reduction in bed days by the expected number of admissions with rifaximin-α + lactulose combination therapy and lactulose monotherapy. The drug costs for rifaximin-α, i.e. the number of months' worth of treatment the hospital provides and, therefore, pays for with the hospital budget is set to one month. Costs related to LT were not taken into account from a hospital perspective, as these costs are covered by healthcare insurance.

The healthcare payer's perspective is that of the Dutch health insurance companies. From the healthcare payer's perspective, the outcome of interest for the cost calculations was the number of hospital admissions and outpatient follow-up visits avoided. Patients were assumed to have one outpatient follow-up visit after discharge from the hospital. Health insurers reimburse a fixed amount per admission and outpatient follow-up visit based on the DBC codes. As mentioned above, the hospital pays for the first month of rifaximin-α and lactulose treatment from the hospital budget. This budget consists of funding provided by insurers, based on DBC codes. In the healthcare payer's perspective, the health insurer pays for the remaining months (from month two

Table 1. Input data for the BI model.

Population	Input value	Source
Dutch adult population	13,924,408	CBS Statline[21]
Dutch cirrhosis prevalence	0.32%	NHG 2016[22], CBS Statline[23]
Point estimate risk of cirrhosis patients experiencing a first episode of overt HE	9%	Vilstrup et al.[1] Calculation: $\frac{\frac{15\%}{5}+15\%}{2}=9\%$
Point estimate risk of patients experiencing a second episode of over HE	64%	Bajaj et al.[7]
Current number of rifaximin-α + lactulose users (in the year 2020)	969 (38%)[a]	GIP databank[16]
Current number of lactulose monotherapy users who are eligible for addition of rifaximin-α (target population)	1,598 (62%)	Calculation: $13,924,408 \times 0.32\% \times 9\% \times 64\% - 969 = 1,598$
Resource use		
Inpatient bed days		Oey et al.[12]
Rifaximin-α + lactulose	3.79 per admission	
Lactulose	8.85 per admission	
Hospital admissions per patient		Oey et al.[12]
Rifaximin-α + lactulose	0.41	
Lactulose	0.86	
LT rate		
Percentage of patients with LT per year	6.1%	Mullen et al.[11]
Mortality rates		
At risk of HE (yearly)		
Rifaximin-α + lactulose	10.8%	Kang et al.[13]
Lactulose	19.0%	Kang et al.[13]
LT (half-yearly)	12.0%	Adam et al.[33]
Post-LT (yearly) [d]	6.4%	Adam et al.[34]
Unit costs	Costs (EUR, 2021)	
Rifaximin-α + lactulose (per month)	€373.39	Dutch drug cost registration[26,25]
Lactulose (per month)	€31.88	Dutch drug cost registration[26,27]
Prescription fee		Medicijnkosten.nl[28]
First prescription	6.50	
Subsequent prescription	13.00	
Hospital cost per bed day	€514.78	Dutch costing manual[29]
Hospital admission cost	€8,200[b]	Dutch Healthcare Authority[31]
Outpatient follow-up visit cost	€255.00[c]	Dutch Healthcare Authority[31]
LT cost (one time cost)	€100,782	Van der Hilst et al.[32]
LT follow-up cost per 6 months[e]	€4,711	Van der Hilst et al.[32]

Abbreviations. HE, hepatic encephalopathy; LT, liver transplantation.
[a]Extrapolated based on an equal growth rate and the number of users in 2018 and 2019.
[b]Hospital admission of 6–28 nursing days for disease of the liver. DBC code: 110801007.
[c]One or two policlinic visits for disease of the liver. DBC code: 110801010.
[d]Based on the 5-year survival of cirrhosis patients with LT from Liver Transplant Registry data of the last 15 years.
[e]Based on the average of donation after cardiac death and donation after brain death.

onwards) of prescriptions. Costs related to LT were taken into account from a healthcare payer's perspective, as these costs are covered by healthcare insurance.

No societal perspective was considered and therefore indirect HE-related costs, such as road accidents, falls, informal care, and productivity losses were not assessed.

Input and data sources

All model input data are provided in Table 1.

Costs

For all costs, we used Dutch data, and values given in price levels different from 2021 were inflated accordingly[24]. The treatment costs of rifaximin-α have been calculated as monthly treatment costs in the Netherlands in 2021. Based on the recommended daily dose from the Summary of Product Characteristics, all patients required two doses of 550 mg per day of one tablet per dose[25]. The drug cost of rifaximin-α was calculated based on the price per pack, as reported in the Dutch drug cost registration (Z-index)[26]. The drug cost of lactulose was calculated based on the average price per ml of all available lactulose syrups in the Z-index, multiplied by the recommended dose 30 ml three times daily[27]. The monthly treatment cost for each treatment was calculated by the following formulas:

$$\text{Monthly treatment cost of rifaximin-}\alpha: = \frac{(\text{dose per administration} \times \text{doses per day})}{\text{pack size}} \times \left(\frac{365.25 \text{ days}}{12 \text{ months}}\right) \times \text{price per pack}$$

$$\text{Monthly treatment cost of lactulose}: = \text{dose per administration} \times \text{doses per day} \times \left(\frac{365.25 \text{ days}}{12 \text{ months}}\right) \times \text{price per ml}$$

The drug costs for rifaximin-α and lactulose for the first month after initiation were assumed to be covered by the hospital. This implies that in both perspectives the hospital pays for the first month of prescriptions. In the healthcare payer's perspective, the health insurer pays for the remaining months (from month two onwards) of prescriptions. No wastage of medication for either rifaximin-α or lactulose from the hospital perspective was assumed i.e. patients will use their entire supply of rifaximin-α or lactulose before moving on to the next pack. However, when patients die, it was assumed the rest of their medication is wasted, and charges for the full supply were still incurred. Prescription fees were also included from the healthcare payer's perspective, whereby the health insurer pays a fee of €13.00 for the first prescription and €6.50 for subsequent prescriptions[28]. Prescription fees were assumed to be charged per medication (one charge for lactulose and one charge for rifaximin-α) and were based on the drug cost registration from the National Health Care Institute, which is in line with the recommendations of the Dutch costing manual[29]. In the base case model, patients are assumed to receive three months' worth of treatment at a time, so in this case there would be six prescription fees charged per drug per cycle, one for each month. Drug costs and prescription fees were only taken into account for patients in the health state "At risk of HE". Patients undergoing LT are no longer at risk of HE and rifaximin-α and lactulose is discontinued.

The hospital cost per bed day, used for the hospital perspective, was based on the tariff from the Dutch costing manual, which reflects the actual costs for the hospital per bed day[29]. For the healthcare payer's perspective calculations, the hospital admission cost was based on the DBC tariff for liver disease-related stays lasting 6–28 days[30]. The cost for outpatient follow-up visits was based on the DBC tariff for a polyclinic visit for liver disease[31]. The one-time cost for LT was based on a prospective costing study in the Netherlands, as not all tariffs for LT-related DBC codes were publicly available[32]. The half-yearly follow-up costs of LT were based on the costs for immunosuppressants from the same study. Costs related to LT were only taken into account from a healthcare payer's perspective, as these costs are covered by healthcare insurance. In accordance with ISPOR's Principles of Good Practice for Budget Impact Analysis guidelines, no discounting has been applied in this budget impact analysis[20].

Resource use

The key data source used to derive efficacy data on resource use was a prospective real-world study in the Erasmus University Medical Center, Rotterdam. This Dutch study consisted of 127 HE patients who received rifaximin-α for secondary prophylaxis of HE and were adherent to treatment. Patients were followed for at least 6 months after rifaximin-α initiation, or until death, liver transplantation, or permanent discontinuation of rifaximin-α occurred. Liver disease severity was graded using Model for End-stage Liver Disease (MELD) and Child-Pugh scores. Patients had a median Child-Pugh number of 8.0 (IQR 7.0–10.0) and a median MELD score of 15.0 (IQR 12.1–20.4)[12]. This is a prospective real-world study in the Netherlands where – though not mentioned explicitly – would likely have been treated according to reimbursement conditions of rifaximin-α, so after the second episode of overt HE. The rates for bed days per admission and hospitalizations per patient were reported per six months (prior to and after rifaximin-α initiation). This was in line with the cycle length of the budget impact model. The outcome of interest for calculating the event costs from the hospital perspective was the number of bed days avoided. The outcomes of interest for calculating the event costs from a healthcare payer's perspective was the number of hospitalizations avoided.

Liver transplantation rates

The target population in our model includes patients who are eligible for LT. After LT, patients are no longer at risk of HE and rifaximin-α and lactulose is discontinued. The LT rate was based on the percentage of patients with LT per year from the rifaximin-α clinical Phase III trial[11]. We have used the following formula to calculate the half-yearly rate from the yearly LT rate:

$$\text{Half yearly LT rate} = 1 - (1 - (\text{yearly LT rate}))^{\frac{1}{2}}.$$

Mortality rates

The mortality for patients in the "At risk of HE" state treated with rifaximin-α + lactulose combination therapy and lactulose monotherapy were based on a retrospective study with over 1,000 patients with overt HE with or without hepatocellular carcinoma[13]. In the population without hepatocellular carcinoma, 145 patients received rifaximin-α (with lactulose) and 276 patients received lactulose monotherapy. 53 out of 145 patients died in the rifaximin-α and 157 out of 276 patients died in the lactulose group with an follow-up time of 48 months. These event rates were converted to yearly mortality transition probabilities: $1 - \left(1 - \left(\frac{53}{145}\right)\right)^{\frac{12}{48}} = 10.8\%$ for rifaximin-α + lactulose and $1 - \left(1 - \left(\frac{157}{276}\right)\right)^{\frac{12}{48}} = 19.0\%$ for lactulose monotherapy. The mortality rates for patients in the "LT" and "post-LT" health states were based on reports from the European Liver Transplantation Registry, including data from the Netherlands[33,34]. 12% of patients die in the first six months after LT. After the first six months, the yearly mortality rate was 6.4%. We have used the following formula to calculate half-yearly rates from the yearly mortality rates:

$$\text{Half yearly mortality rate} = 1 - (1 - (\text{yearly mortality rate}))^{\frac{1}{2}}$$

Background mortality was not included within the model but would be expected to have only a small impact, as it would apply to both treatment arms and only a short time horizon (5 years) is considered in the model.

Analytic framework description

Figure 2 represents the analytic framework of the budget impact analysis. The target population in the model is calculated based on prevalence data. For the target population the total resource use was calculated and multiplied by the unit costs. The resource use and unit costs were stable across

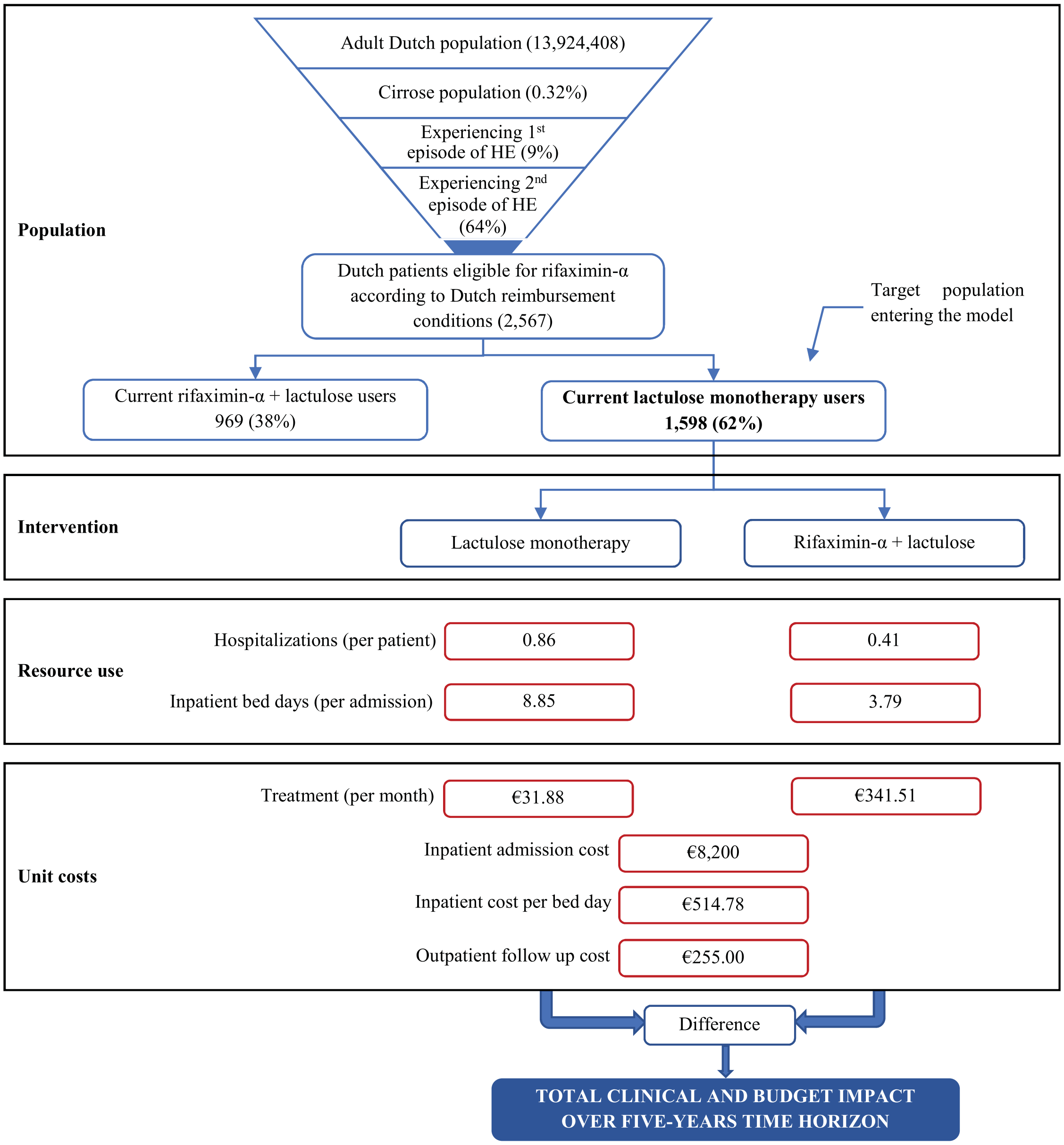

Figure 2. Analytical framework of the budget impact analysis. Abbreviation. HE, hepatic encephalopathy.

the 5-year time horizon. By combining the population, resource use per intervention mix, and the unit costs, the total clinical and budget impact costs were calculated over the time horizon of 5 years.

Uncertainty and analyses

To assess the impact of uncertainty in input parameters on the budget impact, we have performed a univariate sensitivity analysis. The parameters included in the univariate sensitivity analysis are listed in Table 2. Key parameters were varied one by one from their default values by ±25% when the original source of the parameter did not provide a range of uncertainty, while holding other inputs at the base case values. The upper and lower values of the prevalence of cirrhosis were based on diagnosis codes: ICPC (0.44%) and ICD-9 (0.20%), respectively[22,23]. For the percentage of cirrhosis patients with a first episode of overt HE, we used the range of 5–15%, based on the AASLD/EASL guideline[3]. The lower bound of 3% was not possible given the number of currently known rifaximin-α patients, therefore we assumed a lower bound of 5%. The upper value of the percentage of lactulose-treated patients experiencing a second episode of overt HE was based on the percentage found in the total population, including non-adherent lactulose-treated patients[3]. We have used five different methods to extrapolate the number of patients treated with rifaximin-α + lactulose to 2021. Extrapolation based on growth in the previous year has been used in the base case because it gave the median value. The logarithmic extrapolation and a Compound Annual Growth Rate extrapolation gave the lowest and highest values, respectively. Therefore, these have been used as the lower and upper values for the sensitivity analysis, respectively. The results of the univariate sensitivity analysis are presented in a tornado diagram.

Additionally, we conducted five scenario analyses. The mortality rate is relatively higher for the patients treated with

Table 2. Parameters and ranges in the univariate sensitivity analysis.

Parameter	Lower	Base case	Upper	Source
Prevalence of cirrhosis	0.20%[a]	0.32%	0.44%[b]	NHG[22] Dutch Statistics[23]
Percentage of cirrhosis patients experiencing a first episode of overt HE	5.0%[c]	9.0%	15.0%[c]	AASLD/EASL guideline (Vilstrup et al.)[1]
Percentage of patients experiencing a second episode of overt HE	51.2%	64.0%	75.0%[d]	Bajaj et al.[7]
Number of patients currently treated with rifaximin-α + lactulose	948[e]	969	1,092[f]	GIPdatabank[16]
LT rate	5.0%	6.1%	8.0%	Mullen et al.[11]
Mortality rate At risk of HE rifaximin-α + lactulose (yearly)	8.1%	10.8%	13.5%	Kang et al.[13]
Mortality rate At risk of HE lactulose (yearly)	14.3%	19.0%	23.8%	
Mortality rate LT (half yearly)	9.0%	12.0%	15.0%	Adam et al.[33]
Mortality rate post-LT (yearly)	4.8%	6.4%	7.9%	Adam et al.[34]
Bed days per admission rifaximin-α + lactulose	2.84	3.79	4.74	Oey et al.[12]
Bed days per admission lactulose	6.64	8.85	11.06	
Hospital admissions per patient rifaximin-α + lactulose	0.31	0.41	0.51	
Hospital admissions per patient lactulose	0.65	0.86	1.08	
Hospital cost per bed day	€386	€515	€643	Dutch costing manual[29]
Hospital admission cost	€6,176	€8,200	€10,294	DIS open data[30]
Outpatient follow-up visit cost	€191	€255	€319	DIS open data[31]
LT cost	€75,587	€100,782	€125,978	Van der Hilst et al.[32]
Post-LT cost	€3,533	€4,711	€5,888	Van der Hilst et al.[32]

Abbreviations. AASLD/EASL, American Association for the Study of Liver Diseases/European Association for the Study of the Liver; HE, hepatic encephalopathy; ICD. International Statistical Classification of Diseases and Related Health Problems; ICPC, International Classification of Primary Care; LT, liver transplantation; NHG. Dutch College of General Practitioners.
[a]Based on the ICPC-code for cirrhosis/other liver disease, mentioned in the NHG guideline for liver disease.
[b]Based on the ICD-9 code for liver cirrhosis reported by Dutch Statistics.
[c]Based on a lower value of 5% and a maximum average of 15%, respectively, according to the AASLD/EASL guideline (Vilstrup et al.[1]).
[d]Based on the total population (including non-adherent lactulose-treated patients) from Bajaj et al.[7]
[e]Based on logarithmic extrapolation from GIP databank.
[f]Based on Compound Annual Growth Rate extrapolation from GIP databank.

lactulose monotherapy. Therefore, the number of patients alive, who are at risk of HE-related complications and LT, decreased more over time for the lactulose monotherapy than for the patients treated with rifaximin-α + lactulose combination therapy. To account for the health economic pitfall "the cheapest patient is a dead patient" we have included scenario 1, where the influence of an equal yearly mortality rate for the rifaximin-α + lactulose group to the lactulose monotherapy group of 19.0% on the budget impact results was assessed for the healthcare payer's perspective. Additionally, the effect of the prevalence of cirrhosis and the percentage of patients experiencing a first episode of overt HE was assessed from the hospital and healthcare payer's perspectives (scenario 2). Freed-up beds provide hospitals with an opportunity for cost savings, but only if utilized for the treatment of other patients. Therefore, we performed a scenario analysis where we assumed that only half of the freed-up capacity can be reallocated to new patient care (scenario 3). To show the difference in budget impact between a static cohort based on HE prevalence numbers (base case) and a growing cohort based on HE incidence numbers, we have included a scenario where our initial cohort grows annually based on the incidence of HE (scenario 4). The incidence rate was based on the ICPC-code for cirrhosis/other liver disease, mentioned in the Dutch general practitioners' guideline for liver disease (0.06%)[22]. Finally, a scenario wherein the uptake of rifaximin-α was varied from 0 to 100% has been included (scenario 5).

Results

Clinical impact

The number of events that could be prevented with rifaximin-α as an adjunct to lactulose for the prevention of the third and subsequent episodes of overt HE was based on resource use from the real-world study in the Erasmus University Medical Center, Rotterdam[12]. Based on the estimated population of Dutch eligible HE patients, rifaximin-α + lactulose combination therapy could potentially prevent a total of 14,859 hospital bed days and 3,083 hospital admissions compared with lactulose monotherapy over a 5-year period (Table 3). Additionally, 299 deaths could be avoided. In the first six months of the model a total of 3,042 hospital bed days, 657 hospital admissions, and 36 deaths were avoided with rifaximin-α + lactulose combination therapy compared with lactulose monotherapy. The results per year for the clinical impact can be found in Supplementary Appendix 1.

Economic impact

Hospital perspective

Savings per patient from a hospital perspective are €4,487 over a 5-year period. Based on the estimated population of Dutch eligible HE patients, the total hospital costs for rifaximin-α + lactulose combination therapy is 9.0 million euros. This is lower than the total costs of 16.1 million euros with lactulose monotherapy, resulting in total potential cost savings of 7.2 million euros over a 5-year period (Table 3). Although the total budget impact over 5 years is cost-saving, the budget savings decrease in time: −€2,391,491 (2020), −€1,984,655 (2021), −€1,344,280 (2022), −€886,082 (2024), and −€561,293 (2024). The results per year for all model outcomes can be found in Supplementary Appendix 1. The budget impact is mainly driven by the difference in costs related to the hospital bed days (Figure 3). Drug costs have a minimal effect on the total incremental costs, as these are only paid by the hospital for the first month after the initiation of rifaximin-α. The total cost saving over a six-month time horizon was €1,084,711.

Healthcare payer's perspective

Costs per patient from a healthcare payer's perspective are €249 over a 5-year period. Based on the estimated population of Dutch eligible HE patients, the total costs from a healthcare payer's perspective with rifaximin-α + lactulose are 95.8 million euros. This is higher than the costs of 95.4 million euros with lactulose monotherapy, resulting in total incremental costs of 397,770 euros over a 5-year period (Table 3). The total incremental costs from the healthcare payer's perspective are mainly driven by the incremental drug and LT-related costs, which exceed the savings related to hospital admissions avoided by rifaximin-α + lactulose combination therapy (Figure 4). However, in years 2020, 2021 and 2022, savings related to the avoided hospitalizations still exceed the drug and LT-related costs, though budget savings decrease over time: −€4,605,081 (2020), −€1,759,840 (2021), −€217,666 (2022). Eventually in years 2023 and 2024 the drug and LT-related costs exceed the savings: €763,907 (2023) and €1,352,240 (2024). The results per year for all model outcomes can be found in Supplementary Appendix 1. The increasing costs relative to the decreasing savings could be caused by the higher number of patients alive (and therefore at risk of hospitalization and LT) in the rifaximin-α + lactulose treated patients, resulting in incremental drug and LT-related costs and a reduction in hospital admission-related costs. Out-patient visits have a minimal effect on incremental costs. The total cost saving over a six-month time horizon was €2,911,029.

Sensitivity and scenario analyses

Figure 5 represents the results from the univariate sensitivity analysis from a hospital perspective, in which each input parameter in the model was varied individually over their range of uncertainty. The univariate sensitivity analysis shows that the percentage of cirrhosis patients experiencing first episode of overt HE, prevalence of cirrhosis and the number of bed days per admission for lactulose monotherapy have the greatest influence on the incremental total costs from a hospital perspective. The parameters with the greatest influence on the results from a healthcare payer's perspective are the hospital admissions per patient treated with lactulose and rifaximin-α + lactulose and the yearly mortality rate for lactulose-treated patients in the first year (Figure 6).

Results of scenario 1, assuming an equal mortality rate for the rifaximin-α + lactulose and the lactulose monotherapy treated patients for the healthcare payer's perspective,

Table 3. Base case results for 5 years from a hospital and healthcare payer's perspective.

	Rifaximin-α + lactulose	Lactulose	Incremental
Clinical impact			
Number of hospital bed days	16,365	31,224	−14,859
Number hospital admissions	4,318	7,400	−3,083
Number of deaths	660	960	−299
Economic impact			
Hospital perspective			
Total costs	€8,953,199	€16,120,999	−€7,167,800
Drug costs	€528,966	€47,594	€481,372
Costs of hospital bed days	€8,424,233	€16,073,405	−€7,649,172
Costs per patient	€5,604	€10,091	−€4,487
Healthcare payer's perspective			
Total costs	€95,832,188	€95,434,418	€397,770
Drug costs	€23,316,488	€1,719,786	€21,596,702
Costs of hospital admissions	€35,406,535	€60,683,621	−€25,277,086
Costs of outpatient visits	€1,101,057	€1,887,113	−€786,056
Costs of LT (incl. follow-up costs)	€36,008,108	€31,143,898	€4,864,210
Costs per patient	€59,987	€59,738	€249

Abbreviation. LT, liver transplantation.

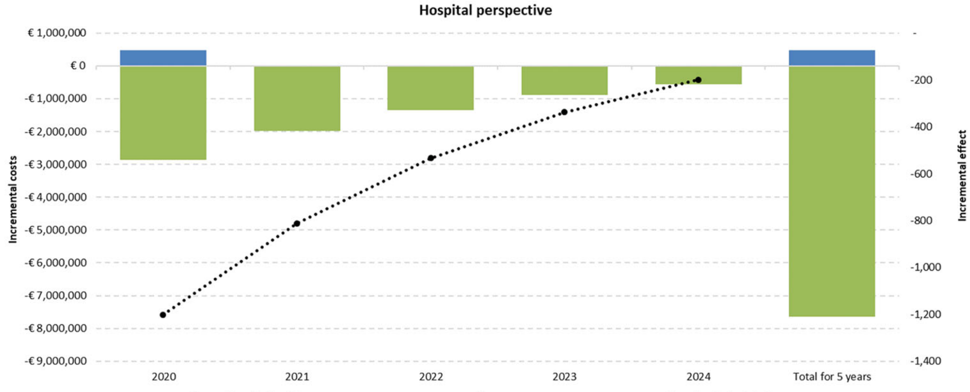

Figure 3. The incremental costs and events, presented by category over a 5-year time horizon from a hospital perspective.

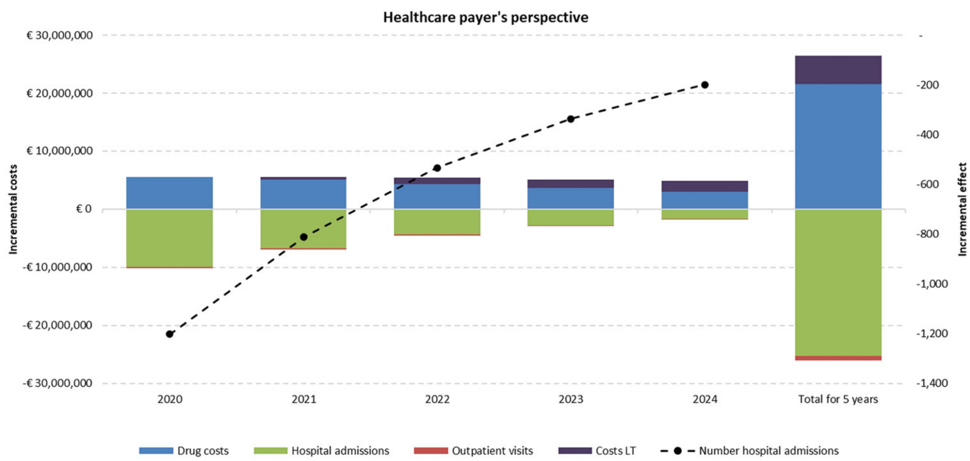

Figure 4. The incremental costs and events, presented by category over a 5-year time horizon from a healthcare payer's perspective. Abbreviation. LT, liver transplantation.

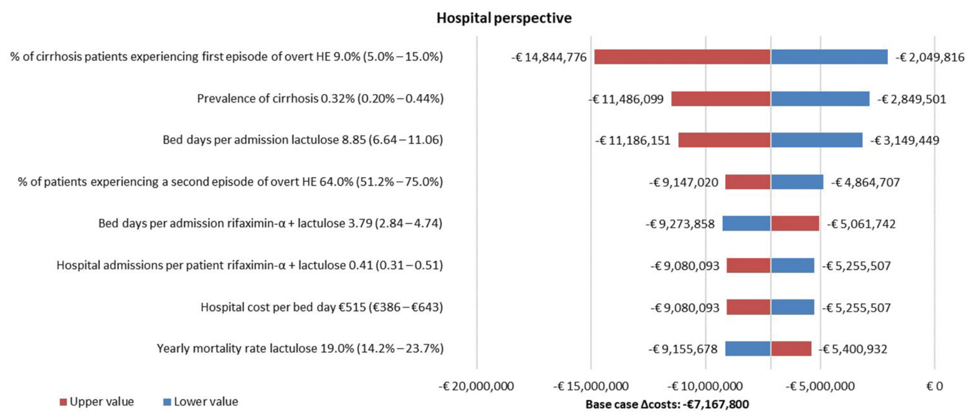

Figure 5. Tornado diagram from the univariate sensitivity analysis for the hospital perspective. Abbreviation. HE, hepatic encephalopathy.

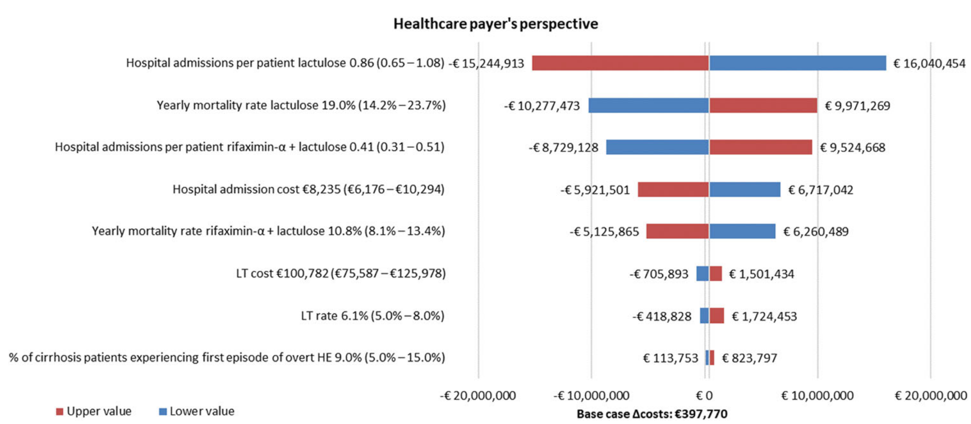

Figure 6. Tornado diagram from the univariate sensitivity analysis for the healthcare payer's perspective. Abbreviations. HE, hepatic encephalopathy; LT, liver transplantation.

showed total cost savings of €15,496,401 (€9,700 per patient). Cost savings related to hospital admissions remain greater than the drug costs for each year of the 5-year time horizon and the difference in LT-related costs is €0 (Figure 7).

Scenario 2 varied the prevalence of cirrhosis and the percentage of patients experiencing a first episode of overt HE between 0.20% and 0.44%, and between 5.0% and 15.0%, respectively (Figure 8). From a hospital perspective, rifaximin-α + lactulose combination therapy remained cost saving compared with lactulose monotherapy. The costs from a healthcare payer's perspective increase with the prevalence, with a maximum of 823,797 euros for situation D (prevalence of cirrhosis of 0.32% and 15.0% of patients experiencing a first episode of overt HE).

In scenario 3 only half of the freed-up hospital beds are reallocated to new patient care. Table 4 shows the cost savings in this scenario analysis. In this scenario cost savings per patient are €967 and total cost savings are €2,025,608 over a 5-year period from a hospital perspective.

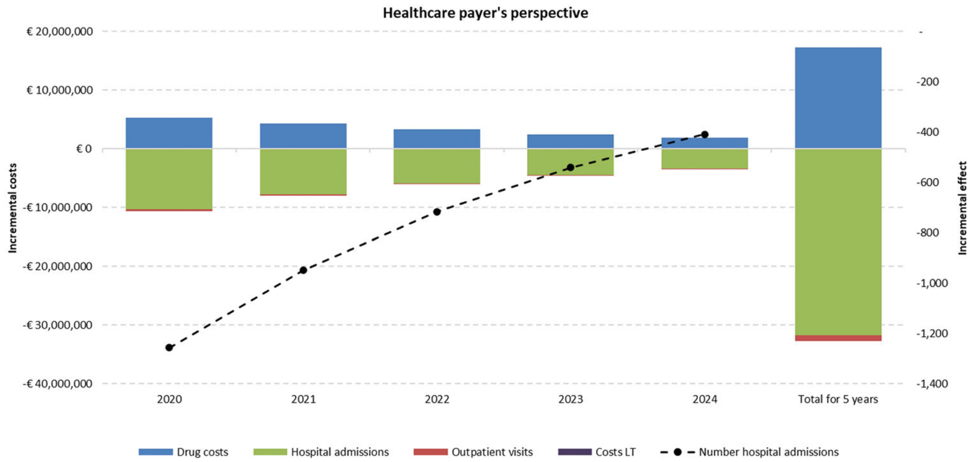

Figure 7. Result of the scenario 1 – assuming an equal number of patients in the "alive" health state at the beginning of each cycle in the Markov model for the rifaximin-α + lactulose and the lactulose monotherapy treated patients for the healthcare payer's perspective. Abbreviation. LT, liver transplantation.

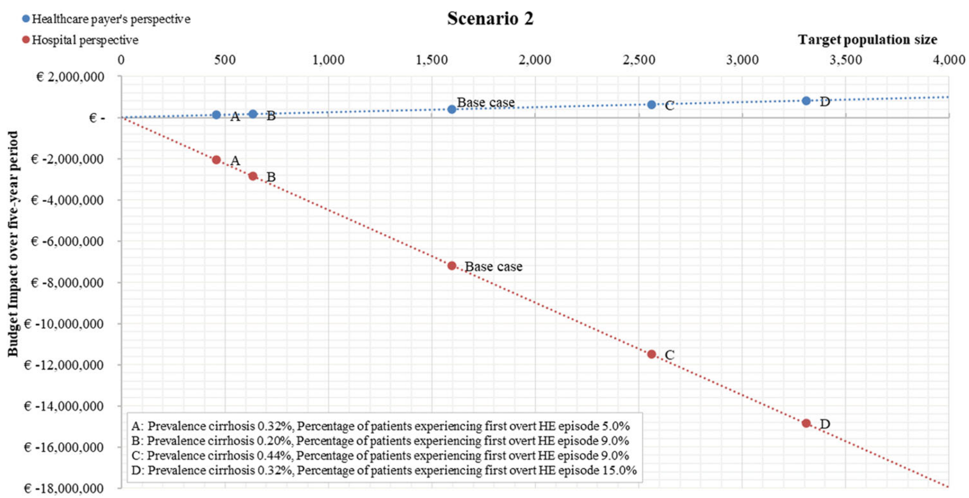

Figure 8. Results of scenario 2 – varying the prevalence of cirrhosis and the percentage of patients experiencing a first episode of overt HE for the hospital and healthcare payer's perspective. Abbreviation. HE, hepatic encephalopathy.

Table 4. Results of scenario 3 – half of freed-up hospital beds are reallocated to new patient care.

	Rifaximin-α + lactulose	Lactulose	Incremental
Hospital perspective			
Costs per patient	€9,124	€10,091	−€967
Total costs	€14,576,763	€16,120,999	−€1,544,235
Drug costs	€528,966	€47,594	€481,372
Costs of hospital bed days	€14,047,797	€16,073,405	−€2,025,608

Scenario 4 shows the effect of the inclusion of incidence rates for HE in the model (Figures 9 and 10). The total incremental budget impact decreases to −€15,378,833 and −€6,755,984 from hospital and healthcare payer's perspectives, respectively. Figure 11 represents the results of scenario 5, where the uptake of rifaximin-α is varied from 0 to 100%. A lower uptake results in a lower total budget impact.

Discussion

This budget impact analysis has shown that the addition of rifaximin-α to lactulose for the prevention of third or subsequent episodes of overt HE can save €4,487 from a hospital perspective and costs an additional €249 from a healthcare payer's perspective per patient over a 5-year period compared with lactulose monotherapy. Currently, an estimated 38% of eligible patients according to the Dutch reimbursement conditions are treated with rifaximin-α + lactulose combination therapy[16]. We calculated the budget impact of treating the remaining 62% of the eligible patients with rifaximin-α + lactulose combination therapy who are currently treated with lactulose monotherapy, i.e. a complete uptake. The base case analysis showed lower resource utilization and results (despite an increase in drug costs) in a total potential cost saving over a 5-year period of 7.2 million euros from a Dutch hospital perspective. The total budget impact is 397,770 euros from a healthcare payer's perspective. Cost savings are driven by the reduction in hospital bed days (−14,859) and hospital admissions (−3,083). Moreover, the addition of rifaximin-α to lactulose could lead to 299 fewer deaths over a 5-year period, underlining the potential health gains of rifaximin-α combination therapy.

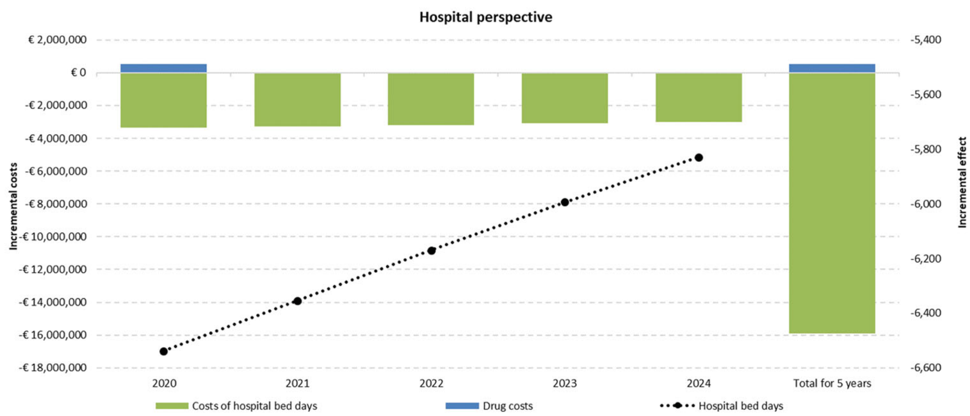

Figure 9. Results of scenario 4 – cohort of HE patients grows annually with incident HE patients from a hospital perspective.

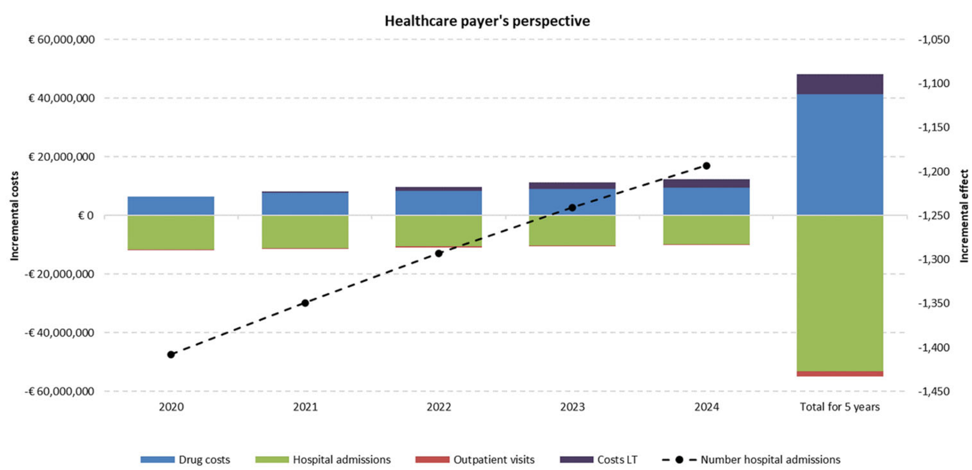

Figure 10. Results of scenario 4 – cohort of HE patients grows annually with incident HE patients from a healthcare payer's perspective.

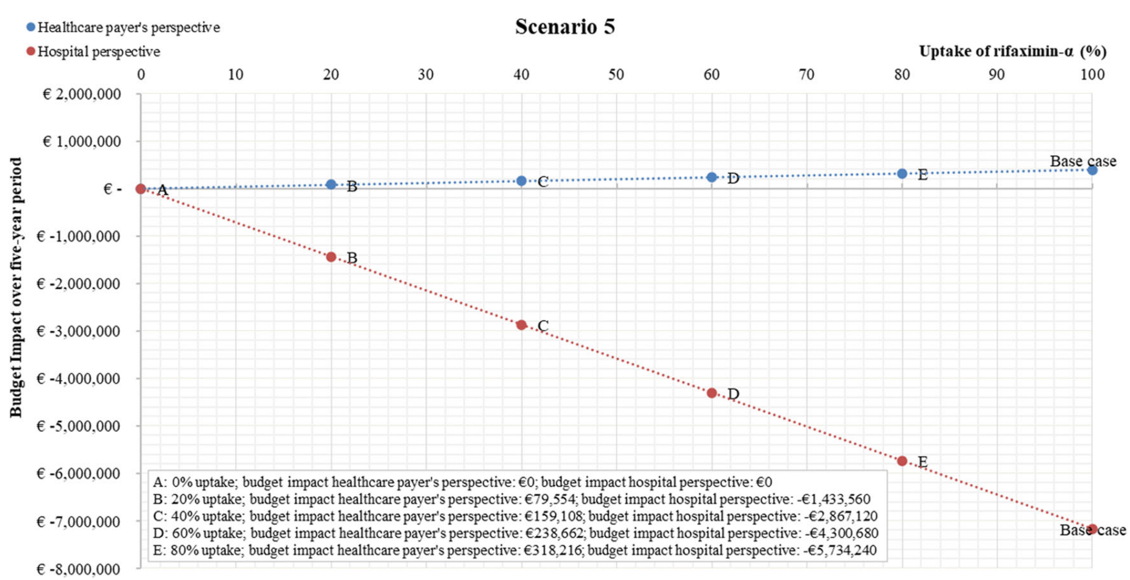

Figure 11. Results of scenario 5 – uptake of rifaximin-α is varied from 0% to 100%.

There are several other cost studies published comparing rifaximin-α + lactulose versus lactulose monotherapy and showing favorable pharmacoeconomic profiles for rifaximin-α[5,17,18]. All cost-effectiveness studies concluded that rifaximin-α treatment has a positive effect on the quality of life. However, partly in contradiction to our results, most of these studies found that improved quality of life is associated with increased costs. A Dutch cost-effectiveness study presented at the European ISPOR conference in 2015 estimated a total incremental cost of €5,418 per patient over a 5-year period from a societal perspective[35]. Though we found increased costs from a healthcare payer's perspective (€249 euros per patient), these costs were much lower than the total incremental costs found in the cost-effectiveness analysis. The difference with our results may be explained by the use of different sources for the relative effectiveness on resource use. Our study was based on Dutch real-world data from the Erasmus University Medical Center, which had not been published in 2015[12], whereas the previous study utilized trial data. Additionally, the use of different perspectives and model structure may lead to different results. Finally, drug prices for rifaximin-α have dropped over time (from €354 in 2015 to €314 in 2021)[26].

On the other hand, there are some cost studies that, despite an increase in drug costs, do show cost-savings related to rifaximin-α + lactulose compared with lactulose monotherapy. A cost-effectiveness study from the same authors as the Dutch cost-effectiveness study, showed savings of £573 (€663) per patient from a United Kingdom (UK) National Health Service perspective over a 5-year period[18]. Moreover, a budget impact analysis conducted from an Italian National Health Service perspective calculated a reduction in total costs of €130,000 after 1 year in 5,000 patients to €320,000 after 3 years time in 7,000 patients[19].

A major strength of this study is that we used a healthcare payer's as well as a hospital perspective. The budget impact analysis was conducted in accordance with ISPOR's Principles of Good Practice for Budget Impact Analysis and the Dutch guideline for economic evaluations in healthcare, which recommend the use of a healthcare payer's perspective[20]. However, this perspective is most relevant when used for reimbursement purposes. Rifaximin-α was approved for reimbursement by the Dutch Ministry of Health in 2016[8] and is therefore already being used in Dutch hospitals for some years. The use of both perspectives makes our analysis not only relevant to healthcare payers but also informative for in-hospital decision making. One other study in the UK assessed the real-world hospital resource utilization and its related costs[14]. It showed a reduction in mean annual emergency inpatient admission costs of £6,607 (€7,650) per patient treated with rifaximin-α + lactulose compared with lactulose monotherapy. As demonstrated by our results and substantiated by this UK study, treating all eligible patients with rifaximin-α + lactulose is very likely to be cost-saving from a hospital perspective.

In the base case analysis, patients in the rifaximin-α + lactulose group survive longer compared with the lactulose monotherapy group due to their lower yearly mortality rate. Scenario 1, assessing the effect of an equal mortality rate for rifaximin-α + lactulose combination therapy and lactulose monotherapy treated patients, showed that the increased survival had three effects: (1) a relative higher number of patients at risk of hospital admission over time, causing relative lower hospital admission-related cost savings (2) a relative increase in drug costs, and (3) a higher chance of LT resulting in relative higher LT-related costs for rifaximin-α treated patients. This scenario illustrates that after a specific duration of treatment lactulose may seem less costly and more effective in preventing hospitalization, but this is due to higher mortality in the lactulose arm. Rifaximin-α increases survival which is desirable in terms of the patient's and their caretakers' quality of life. On the other hand, as illustrated by this scenario, it also causes an increase in costs leading to a reduction in potential hospital admission-related cost savings on the long-term, resulting in an overall cost of €397,770 in the base case analysis. Inevitably, while patients are alive, they also incur additional treatment costs associated with liver cirrhosis, which are – apart from LT – not included in this analysis. In this paper we focus on HE-related costs, but it should be mentioned that this phenomenon does also lead to increased cirrhosis-related costs, such as liver cancer costs.

In accordance with the reimbursement conditions that were based on the population included in the initial clinical trials, the target population in the model consisted of adult patients experiencing a second episode of overt HE[10,11]. Though rifaximin-α could in theory also be effective after a first episode of overt HE, there is no data to support this and is currently not being investigated. Neither guidelines nor reimbursement conditions are expected to change in the near future, and therefore this scenario was not considered in our analysis. The size of the target population has been estimated based on a combination of prevalence numbers of cirrhosis and the risk of experiencing a first and subsequently a second episode of overt HE. It was calculated based on literature referred to in guidelines and current best-available data. However, possibly due to differences in definitions or data collection methods, uncertainty remains surrounding these prevalence numbers. To make a reliable estimation, our base case population size was estimated based on values between the upper and lower bounds found in literature. Nevertheless, these inputs showed a great influence on the budget impact results in the univariate sensitivity analysis. Therefore, we conducted a scenario analysis to analyze the effect on the total budget savings of using different sources to calculate the population size (Figure 8). The budget impact per patient remains cost saving from a hospital perspective. However, it should be assessed how acceptance and adoption of rifaximin-α in daily practice can be optimized.

Treatment of all 62% remaining eligible patients who are currently being treated with lactulose monotherapy might be an overestimation since some patients might recover from an episode with the removal of evoking factors and will not be seen by a hospital specialist and thus not prescribed rifaximin-α. However, it is unknown for how many of the patients this is the case. Moreover, many of these patients are repeatedly admitted at a later stage with overt HE without evoking and treatable factors, and the addition of rifaximin-α might prevent part of these admissions. Scenario 5, where the uptake of rifaximin-α was varied from 0% to 100%, showed that even with a low uptake the budget impact is still cost saving from a hospital perspective, as the budget impact per patient remains cost saving. The budget impact from a healthcare payer' remains positive, but does decrease with a lower uptake of rifaximin-α. Nevertheless, it is important to underline that with the base case analysis we illustrate the potential budget impact if the uptake would have been optimal (absolute maximum). In reality, it is likely that the uptake of rifaximin-α is lower.

In our base case analysis, we modelled a static target population based on HE prevalence numbers for simplification on the basis that including more patients each year would only improve the case for rifaximin-α, since it already is cost saving from a hospital perspective. In scenario 4, we demonstrated the effect of a dynamic target population by including incidence rates. The total budget impact for the target population also including incident eligible patients each year, dropped to −15 million euros from a hospital perspective and even became cost saving from a healthcare payer's perspective with a budget impact of −7 million euros.

It was assumed that the hospital would cover the costs of rifaximin-α for the first month after initiation. This is a conservative assumption, since clinical practice rarely shows hospital stays with a duration of one month for patients with an overt HE episode. Thus, rifaximin-α costs covered by the hospital are likely to be lower in clinical practice than the drug costs assumed in the model. On the other hand, we calculated the cost savings from a hospital perspective based on the number of bed days avoided. However, it is uncertain if all freed-up hospital beds as a result of rifaximin-α treatment can be reallocated to new patient care. Scenario 3, where only half of the freed-up hospital beds could be reallocated to new patient care, showed that treatment with rifaximin-α still is beneficial when not every empty hospital bed is needed for other patient care, but cost savings are reduced.

Outpatient follow-up visits were only included in the healthcare payer's perspective, as these visits are declared by the hospital as a separate DBC code for outpatient visits. From the hospital perspective, minimizing these visits does not save costs and therefore these were not included. However, fewer outpatient visits can result in loss of income for the hospital. Nevertheless, the avoided outpatient follow-up visits are assumed to be replaced by other care and should therefore not to be seen as income lost to the hospital.

Rifaximin-α and lactulose are currently the best available preventive treatments for HE in the Netherlands and were, therefore, the comparative treatments in our budget impact model. However, the ANSWER and ATTIRE trials show that albumin infusion therapy could prove useful in patients with chronic decompensated cirrhosis and may potentially also reduce the risk of HE[36–38]. The ANSWER trial also showed that albumin infusion prolongs overall survival. It included rifaximin-α as possible concomitant treatment. Though albumin's potential effect could be relevant for a select subgroup of the target population it is seldomly used in the Netherlands, partly because of the associated costs, but also because the EASL has not recommended its use in their guidelines[1]. As it stands, because it has not been accepted for reimbursement and its general lack of deployment, we have not considered albumin infusion therapy in our analysis.

An important strength of our study is the use of real-world country-specific data to calculate the clinical and economic impact. We based the effect on resource use of rifaximin-α + lactulose compared with lactulose monotherapy on a Dutch real-world study conducted in the Erasmus University Medical Center, Rotterdam[12]. Two other real-world studies on resource use of rifaximin-α + lactulose combination therapy versus lactulose monotherapy for the prevention of HE have been published in the UK. These studies both reported higher absolute numbers for hospital admissions per patient (0.8 and 1.0 for the rifaximin-α + lactulose versus 1.7 and 1.6 for lactulose monotherapy) and length of stay (5.2 and 8.6 for the rifaximin-α + lactulose versus 10.9 and 13.5 for lactulose monotherapy) for both the rifaximin-α + lactulose and lactulose monotherapy groups. However, the absolute reductions caused by the addition of rifaximin-α, which lead to the cost savings, were comparable to the Erasmus study.

Although the Erasmus study is the best available source for the resource use in this model, it also has some limitations. Firstly, it did not include mortality. Therefore, the mortality rates were calculated based on a Korean study in 1,042 patients experiencing HE[13], which may not entirely represent the Dutch HE population as there could be between-country differences in the patient population, disease course, and healthcare provided. On the other hand, the major advantage of this Korean study is that it specifically assessed the effect of rifaximin-α (with lactulose) versus lactulose monotherapy in a real-world setting with a long-term follow-up of 48 months in a relatively high number of patients compared to other studies or clinical trials[39], making it the most suitable study to use for our analysis.

Secondly, resource utilization data on hospital admissions and hospital bed days had to be extrapolated to 5 years, for which we assumed an equal rate over time. This assumption may influence the model results, since the number of hospital admissions and hospital bed days have shown to be the most influential parameters from the hospital and healthcare payer's perspective, respectively. One of the real-world studies conducted in the UK had a follow-up of 12 months, however, there were no major differences between the six- and 12-month results[15]. Moreover, the pivotal Phase 3 trial of rifaximin-α showed a continued reduction in the rate of HE-related and all-cause hospitalizations over a 24-month period[11]. Although it is not known whether the effect of rifaximin-α will be maintained over 5 years, there is no evidence that suggests otherwise. Still, this assumption could potentially have led to an under- or overestimation of the model results. For future research, it could be relevant to collect such data for Dutch patients experiencing overt HE.

Conclusions

To conclude, treating patients who are eligible according to Dutch reimbursement conditions with rifaximin-α as an adjunct to lactulose for the prevention of third and subsequent episodes of overt HE can save €4,487 per patient from a hospital perspective and costs an additional €249 per patient from a healthcare payer's perspective. Currently, around 38% of the estimated eligible patients are treated with rifaximin-α. The patient, as well as the hospital, could benefit from optimizing the use of rifaximin-α as an adjunct to lactulose for the prevention of third and subsequent episodes of overt HE in the Netherlands. From a healthcare payer's perspective, costs increase with addition of rifaximin-α to lactulose due to the relative better survival with rifaximin-α, causing relatively higher drug and liver transplantation-related costs.

Note

i. XIFAXAN is a registered trademark of Norgine B.V., Amsterdam, Netherlands.

Transparency

Declaration of funding

This work was supported by the Norgine. LADJ, AVVS, HSH, and BVH declare to have no conflict of interest.

Declaration of financial/other interests

LADJ, AVVS, and HSH are employed by Asc Academics. MJP reports grants and honoraria from various pharmaceutical companies, all unrelated to this study.

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Author contributions

LADJ, HSH, MJP, and BVH were involved in the conception and design of the study.

All authors were involved in the interpretation of the data.

LADJ, AVVS, and HSH drafted the paper.

MJP and BVH critically appraised the paper for its content.

All authors approved of the final version of the work published.

All authors agreed to be accountable for all aspects of the work.

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References

[1] Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–735.

[2] Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther. 2007;25 (Suppl 1):3–9.

[3] Kerbert AJC, Reverter E, Verbruggen L, et al. Impact of hepatic encephalopathy on liver transplant waiting list mortality in regions with different transplantation rates. Clin Transplant. 2018;32(11):e13412–8.

[4] Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol. 2011;106(9):1646–1653.

[5] Neff G, Zachry W. III. Systematic review of the economic burden of overt hepatic encephalopathy and pharmacoeconomic impact of rifaximin. Pharmacoeconomics. 2018;36(7):809–822.

[6] National Health Care Institute – Farmacotherapeutisch Kompas. Lactulose. [cited 2021 May 20]. Available from: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/l/lactulose#indicaties.

[7] Bajaj JS, Sanyal AJ, Bell D, et al. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Aliment Pharmacol Ther. 2010;31(9):1012–1017.

[8] National Health Care Institute. Reassessment of rifaximin (Xifaxan) for overt hepatic encephalopathy. 2016. [cited 2021 May 20]. Available from: https://www.zorginstituutnederland.nl/publicaties/rapport/2016/04/14/herbeoordeling-rifaximine-xifaxan-bij-manifeste-hepatische-encefalopathie.

[9] National Health Care Institute. Medicijnkosten.nl – XIFAXAN tablet filmomhulde 550mg. [cited 2021 May 20]. Available from: https://www.medicijnkosten.nl/medicijn?artikel=XIFAXAN+TABLET+FILMOMHULD+550MG&id=756c669de9bf33cde99055a52def0eef.

[10] Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071–1081.

[11] Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clin Gastroenterol Hepatol. 2014;12(8):1390–1397.e2.

[12] Oey RC, Buck LEM, Erler NS, et al. The efficacy and safety of rifaximin-α: a 2-year observational study of overt hepatic encephalopathy. Therap Adv Gastroenterol. 2019;12:175628481985825. 1756284819858256.

[13] Kang SH, Lee YB, Lee J-H, et al. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. Aliment Pharmacol Ther. 2017;46(9):845–855.

[14] Orr JG, Currie CJ, Berni E, et al. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-α. Liver Int. 2016;36(9):1295–1303.

[15] Hudson M, Radwan A, Di Maggio P, et al. The impact of rifaximin-α on the hospital resource use associated with the management of patients with hepatic encephalopathy: a retrospective observational study (IMPRESS). Frontline Gastroenterol. 2017;8(4):243–251.

[16] National Health Care Institute – GIPdatabank. Number of users 2015-2019 for ATC-subgroup A07AA11: Rifaximin. [cited 2021 May 1]. Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=gebr&spec=&item=A07AA11.

[17] Jesudian AB, Ahmad M, Bozkaya D, et al. Cost-Effectiveness of rifaximin treatment in patients with hepatic encephalopathy. J Manag Care Spec Pharm. 2020;26(6):750–757.

[18] Berni E, Murphy D, Whitehouse J, et al. Evaluation of the cost-effectiveness of rifaximin-α for the management of patients with hepatic encephalopathy in the United Kingdom. Curr Med Res Opin. 2018;34(11):2001–2008.

[19] Roggeri DP, Roggeri A. Economic impact of the use of rifaximin 550 mg twice daily for the treatment of overt hepatic encephalopathy in Italy. Hepat Med. 2017;9:37–43.

[20] Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012

budget impact analysis good practice II task force. Value Health. 2014;17(1):5–14.
[21] Dutch Statistics CBS Statline. Dutch adult population. [cited 2021 May 1]. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37296ned/table?fromstatweb.
[22] Dutch College of General Practitioners (NHG). Virushepatitis en andere leveraandoeningen. 2016. [cited 2021 May 20]. Available from: https://richtlijnen.nhg.org/standaarden/virushepatitis-en-andere-leveraandoeningen.
[23] Dutch Statistics (CBS StatLine). Health and healthcare use: patient characteristics. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83005NED/table?fromstatweb.
[24] Dutch Statistics (CBS StatLine). Consumer index prices from 1963. [cited 2021 Apr 4]. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70936NED/table?fromstatweb.
[25] Summary of Product Characteristics rifaximin-α (Xifaxan®). [cited 2021 May 11]. Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h110659_smpc.pdf.
[26] Z-index February 2021. https://www.z-index.nl/.
[27] National Health Care Institute – Farmacotherapeutisch Kompas. [cited 2021 May 11]. Available from: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/l/lactulose#dosering.
[28] National Health Care Institute. Medicijnkosten.nl. – About. [cited 2021 May 1]. Available from: https://www.medicijnkosten.nl/toelichting.
[29] Hakkaart-van Roijen L, van der Linden N, Bouwmans C, et al. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Dutch National Health Care Institute. 2016:1–73.
[30] Dutch Healthcare Authority (NZa). Declaration code: 110801007. [cited 2021 Apr 6]. Available from: https://www.opendisdata.nl/msz/zorgproduct/110801007.
[31] Dutch Healthcare Authority (NZa). Declaration code: 110801010. [cited 2021 Apr 6]. https://www.opendisdata.nl/msz/zorgproduct/110801010?.
[32] van der Hilst CS, Ijtsma AJ, Bottema JT, et al. The price of donation after cardiac death in liver transplantation: a prospective cost-effectiveness study. Transpl Int. 2013;26(4):411–418.
[33] Adam R, Karam V, Delvart V, et al. European Liver and Intestine Transplant Association (ELITA). evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675–688.
[34] Adam R, Karam V, Cailliez V, et al. 2018 Annual report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. Transpl Int. 2018;31(12):1293–1317.
[35] Whitehouse JT, Berni E, Conway P, et al. PGI38 - evaluation of the cost effectiveness and societal impact of Rifaximin-Á 550mg in the reduction of recurrence of overt hepatic encephalopathy in The Netherlands. Value Health. 2015;18(7):A629.
[36] Caraceni P, Riggio O, Angeli P, et al. ANSWER study investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet. 2018;391(10138):2417–2429.
[37] Caraceni P, Abraldes JG, Ginès P, et al. The search for disease-modifying agents in decompensated cirrhosis: from drug repurposing to drug discovery. J Hepatol. 2021;75(Suppl 1):S118–S134.
[38] Teh KB, Loo JH, Tam YC, et al. Efficacy and safety of albumin infusion for overt hepatic encephalopathy: a systematic review and meta-analysis. Dig Liver Dis. 2021;53(7):817–823.
[39] Wang Z, Chu P, Wang W. Combination of rifaximin and lactulose improves clinical efficacy and mortality in patients with hepatic encephalopathy. Drug Des Devel Ther. 2019;13:1–11.