

Public Assessment Report

Scientific discussion

TIXTELLER 550 mg film-coated tablets

(rifaximin)

NL/H/4510/001/DC

Date: 6 August 2019

This module reflects the scientific discussion for the approval of TIXTELLER 550 mg film-coated tablets. The procedure was finalised at 29 November 2012. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for TIXTELLER 550 mg film-coated tablets from Alfa Wassermann S.p.A.

These are prescription-only medicines indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients over ≥ 18 years of age.

A comprehensive description of the indications and posology is given in the SmPC.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Greece, France, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Romania, Slovakia.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

The main studies submitted to support the above application are:

- 1 Pharmacokinetic studies:
 - I. Food-effect, single-dose, and multiple-dose pharmacokinetics study in healthy volunteers RFPK1007
 - II. Efflux transport studies; PK0903 in Caco-2 cells in vitro
 - III. Drug-interaction studies in healthy volunteers RFDI1008 and RFDI1009
 - IV. Pharmacokinetic study of rifaximin in the target population, ie subjects with hepatic cirrhosis and a history of HE; RFHE3002PK. Subjects had mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment.
- 2 Dose finding studies:
 - V. Dose ranging study RFHE9702
 - VI. Phase 3 studies RFHE9701 and RFHE9901, which investigated rifaximin therapy for up to 15 days in subjects with active HE.
- 3 Clinical safety and Efficacy studies:
 - VII. Double-blind 6-month, placebo-controlled study RFHE3001
 - VIII. Open-label study RFHE3002.
- 4 Supportive data:
 - IX. Published meta-analyses
 - X. Published individual clinical trials of rifaximin in patients with HE provide Loguercio et al, Fera et al and Miglio et al which investigated the effectiveness of interventional treatment with rifaximin in subjects with active HE over chronic durations of therapy (3 months or 6 months).

In addition, data from the previous studies submitted in support of the 200 mg tablets (approved for the treatment of Traveller's diarrhoea) as well as clinical studies in other indications are also mentioned.

II. QUALITY ASPECTS

II.1 Drug Substance

rINN:	Rifaximin
Chemical name:	(2S, 16Z, 18E, 20S, 21S, 22R, 23R, 24R, 25S, 26S, 27S, 28E)-5,6,21,23,25-Pentahydroxy-27-methoxy-2,4,11,16,20,22-24,26-octamethyl-2,7-(epoxypentadeca [1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-a]benzimidazole-1,15(2H)-dione, 25-acetate [(2S-[2R*, 16Z, 18E, 20R*, 21R*, 22S*, 23S*, 24S*, 25R*, 26S*,27R*, 28E)]-25-(Acetyloxy)-5,6,21,23-tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-[epoxypentadeca [1,11,13]-trienimino]benzofuro[4,5-e]pyrido[1,2-a] benzimidazole-1,15 (2H)-dione
Molecular formula:	C43H51N3O11 Molecular weight: 786
Appearance:	Red-orange crystalline powder.
Solubility:	Soluble in organic media and insoluble in aqueous media

Rifaximin is the subject of a European Pharmacopoeia monograph.

Rifaximin is a structural analogue of rifampicin. The mechanism of action is similar to that of other rifamycin antibacterial agents involving the inhibition of DNA-dependent RNA polymerase in susceptible bacteria. The selected polymorphic form is insoluble in water and has been selected for use for local treatment.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant

specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.2 Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely sodium starch glycolate type A, glycerol distearate, colloidal anhydrous silica, talc, microcrystalline cellulose, hypromellose, titanium dioxide (E171), disodium edetate, propylene glycol and red iron oxide (E172).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of red iron oxide (E172), which complies with Directive 2001/128/EC, as amended. Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable product containing rifaximin, that could be used for the reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients ≥ 18 years of age.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated using two pilot-scale batches and one industrial-scale batch, and has shown satisfactory results. The marketing authorisation holder has committed to completing validation studies for the first two commercial-scale batches, post authorisation.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply

with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters, which are packed into cartons in pack sizes of 14, 28, 42, 56 and 98 tablets per carton. The marketing authorisation holder has stated that not all pack sizes are intended for marketing. They have committed to providing the relevant licensing authority with the mock-ups for those pack sizes that will be marketed in that country.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no specific storage conditions.

II.3 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that TIXTELLER has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The applicant has demonstrated the activity of rifaximin against a broad range of bacteria, including those bacteria known to produce ammonia. The applicant has suggested that rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy. Clinical evidence in support of the new indication (to reduce the recurrence of hepatic encephalopathy episodes) has been provided. The applicant has investigated the likelihood of development of resistance following the treatment of *M. tuberculosis*-infected patients with rifaximin. In addition, the beneficial effects of rifaximin in an experimental model of colitis have also been demonstrated.

Although rifaximin is poorly absorbed from the gastrointestinal tract, it is noted that the maximum daily dose is higher (1100 mg) than that previously proposed (600 mg). However, the non-clinical data and clinical data available/submitted in support of this application do not indicate an increased probability to interact with secondary pharmacological targets or an increase in the incidence of adverse events. The safety pharmacology studies conducted appear to be adequate to support the maximum proposed dose of 1100 mg per day on the basis of human equivalent dose (but not on the basis of systemic exposures).

III.2 Pharmacokinetics

The data provided suggest that following oral administration, rifaximin is poorly absorbed from the gastrointestinal tract in animals and in man. In the rat, it is confined to the gastrointestinal tract with small amounts in the liver at 24 hours post-dose, which supports its use in the treatment of patients with traveller's diarrhoea and hepatic encephalopathy. Placental transfer of rifaximin has been demonstrated in the pregnant rabbit; however, actual exposure to the fetus was considered to be minimal. The applicant has not investigated whether rifaximin or its metabolites are transferred to maternal milk.

The small proportion of rifaximin that is absorbed following oral administration is metabolised primarily by CYP3A4 and the predominant metabolite was identified as 25-desacetyl rifaximin (which is less pharmacologically active than rifaximin). In animals and in man, the predominant route of excretion is via the feces. The applicant has investigated the effects of rifaximin on a series of drug transporters and has concluded that the potential for pharmacokinetic interactions with concomitantly administered medicinal products is low.

III.3 Toxicology

The maximum non-lethal doses in mice and rats are at least 17-fold and 35-fold higher than the maximum proposed human equivalent dose of rifaximin and the observed safety margins are considered to be acceptable. The series of repeated-dose studies for up to 26 weeks in the rat and up to 39 weeks in the dog support the proposed clinical duration. Alterations in alkaline phosphatase and alanine amino transferase enzymes were observed during the 26-week study in the rat and in the absence of histological changes and as the incidence in liver TEAEs are comparable in the 550 mg BID group when compared to placebo, the applicant considers these changes not to be clinically relevant. It is noted that the increase in liver enzymes was observed at ≥ 150 mg/kg/day, where the observed systemic exposures were lower than those proposed clinically; hence, the non-clinical data available cannot definitively rule out the possibility of such toxicity.

In vitro and in vivo studies demonstrate that rifaximin is not genotoxic. Moreover, the results from the 26-week and 104-week carcinogenicity studies in mice and rats, respectively, suggest that the potential for rifaximin to be carcinogenic is low. A small

increase in the incidence of malignant schwannomas in the endocardial tissue of males at 150/200/250 mg/kg/day was noted (3/60 animals compared to 0-1/60 animals). However, given that the observed difference is small in magnitude and that endocardial schwannomas are known to occur sporadically in the rat; this finding was not considered to be treatment related.

The embryofetal development studies performed in the rat and the rabbit suggest that rifaximin is not teratogenic. However, delayed ossification was observed in the rat at 300 mg/kg/day, while skeletal variations were observed in the rabbit at all doses evaluated (at \geq 62.5 mg/kg/day). The findings from the embryofetal development studies have been captured within Section 4.6 and 5.3 of the SmPC, which is acceptable.

Following repeated administration of rifaximin (for up to 4 weeks), an increase in the numbers of CD4+ and CD8+ T-lymphocytes were observed at \geq 150 and 500 mg/kg/day, respectively. However, no other effects on the immune system of toxicological significance were observed. Moreover, rifaximin did not elicit a sensitisation response in the guinea pig and in man and the incidence of allergic reactions did not appear to increase with dose (up to 1100 mg). Hence, the observed effects on CD4+ and CD8+ T lymphocytes do not appear to be clinically relevant.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The applicant has conducted a series of studies to investigate the potential for ecotoxicity, which are considered to be adequate. The results suggest that rifaximin will not constitute a risk to the environment.

III.5 Discussion on the non-clinical aspects

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

There are no objections to the approval of this product from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

Active intervention studies in subjects with hepatic encephalopathy

Three of the controlled clinical studies included a Phase II, dose-finding study (Study RFHE9702) and two Phase III, double-blind, randomized studies (Studies RFHE9701 and RIF/HE/INT/99). Each of these three studies followed acute treatment regimens (\leq 21 days). Rifaximin treatments resulted in improvements in asterixis severity grade, in the mental

status component of the PSE Index, and in other efficacy endpoints in studies RFHE9702, RFHE9701, and RIF/HE/INT/99.

In study RFHE9701, which compared rifaximin against lactitol, rifaximin was found to be superior to lactitol in several efficacy endpoints, including the primary efficacy endpoint. In study RFHE9702, superior efficacy results were observed with respect to asterixis grades; and, in study RIF/HE/INT/99, similar efficacy results were observed for mental state improvements between rifaximin-treated subjects versus placebo-treated subjects.

Published meta-analyses

A meta-analysis of data from 22 clinical trials of lactulose or lactitol, antibiotics, no intervention, or placebo in the treatment of patients with hepatic encephalopathy showed an inconsistent positive effect of lactulose/lactitol on hepatic encephalopathy symptoms when compared to no intervention or placebo intervention. In the data from studies included in this meta-analysis, antibiotics (aminoglycosides or rifaximin) were found to be statistically superior to lactulose/lactitol in the treatment of hepatic encephalopathy. The authors concluded that available data were insufficient to recommend the use of lactulose/lactitol for hepatic encephalopathy and that lactulose/lactitol should not be used as a comparator in future clinical studies.

In another meta-analysis, 17 clinical trials using rifaximin in patients with hepatic encephalopathy were reviewed for effectiveness in improving behavioral, laboratory, mental status and intellectual abnormalities associated with hepatic encephalopathy. The meta-analysis concluded that rifaximin was as effective, and in some studies, superior, to comparators such as lactulose, lactitol, neomycin, and paromomycin in reducing symptoms of hepatic encephalopathy.

IV.1 Clinical safety and efficacy

Dose-finding study

RFHE9702 evaluated three doses of 600mg, 1200mg and 2400mg of Rifaximin for 7 days in hepatic encephalopathy of Grades I, II and III. Study RFHE9701 compared rifaximin 400mg tid versus lactitol 20g tid, while RFHE 9901 evaluated rifaximin in patients intolerant to lactulose or lactitol. The clinical overview mentioned that the dose of 1100mg (550mg bid) was selected from these studies, as well as other published studies.

Pivotal and long-term studies (RFHE3001 and RFHE3002)

Study RFHE3001 was a Phase III, multicentre, 6-month, double-blind, randomised, placebo-controlled study evaluating the efficacy and safety of rifaximin 550 mg bid as compared to placebo. Subjects in remission (Conn score of 0 or 1) from demonstrated recurrent, overt, episodic hepatic encephalopathy associated with chronic, hepatic cirrhosis were randomised on Day 0 according to a 1:1 ratio to receive rifaximin 550 mg bid or placebo for 6 months.

Subjects discontinued from the study at the time of breakthrough overt hepatic encephalopathy episode.

After participation in study RFHE3001, subjects had the option to enroll in the open-label, treatment extension study (RFHE3002). Study RFHE3002 was a multicentre, open-label, treatment-extension study evaluating the long-term safety and tolerability of rifaximin 550 mg bid administered for at least 24 months in subjects with a history of recurrent, overt, episodic hepatic encephalopathy. Unlike study RFHE3001, subjects with Conn scores of 0, 1, or 2 were eligible for participation, and subjects were not required to withdraw from the study after experiencing a breakthrough overt hepatic encephalopathy episode.

Concomitant lactulose therapy was permitted in studies RFHE3001 and RFHE3002. In RFHE3001, > 90% of subjects in the rifaximin and placebo groups received concomitant lactulose therapy, in RFHE3002 study 88% of patients were administered concomitant lactulose.

Pivotal Study RFHE3001

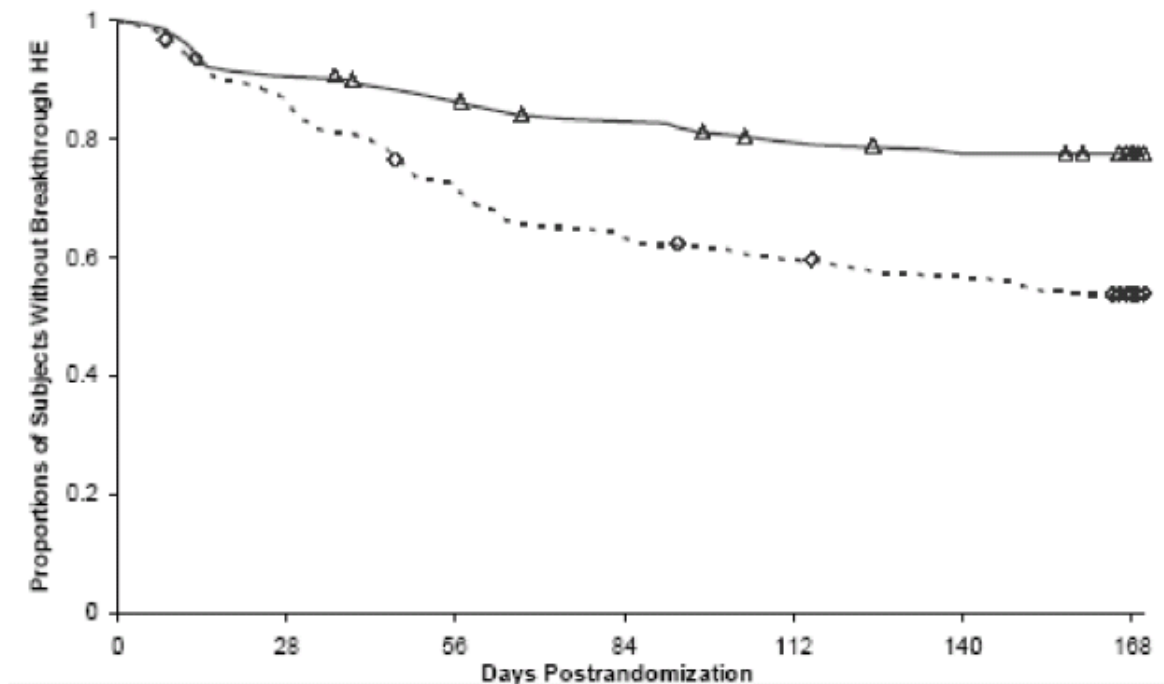
A total of 299 subjects were randomized to receive rifaximin (140 subjects) or placebo (159 subjects)

As specified in the protocol, subjects were to be withdrawn from the study after experiencing a breakthrough overt hepatic encephalopathy episode. Breakthrough overt hepatic encephalopathy episode was the primary reason for early study withdrawal for 28 of 140 subjects (20%) in the rifaximin group and 69 of 159 subjects (43.4%) in the placebo group.

Primary reasons for early study discontinuation other than breakthrough overt hepatic encephalopathy episode were adverse events (15 subjects), subject request (15 subjects), death (9 subjects), development of exclusion criteria (4 subjects), liver transplant (1 subject), and other reason (4 subjects).

Primary efficacy endpoint: time to first breakthrough overt hepatic encephalopathy
Breakthrough overt hepatic encephalopathy episodes were experienced by 31 of 140 subjects in the rifaximin group and by 73 of 159 subjects in the placebo group during the 6-month treatment period (up to Day 170). Comparison of Kaplan-Meier estimates of time to breakthrough overt hepatic encephalopathy between groups showed a highly significant protective effect of rifaximin ($p < 0.0001$). The hazard ratio for the risk of experiencing breakthrough overt hepatic encephalopathy in the rifaximin group relative to the risk in the placebo group was 0.421 (95% confidence interval [CI]: 0.276 to 0.641) during the 6-month treatment period. These data show that rifaximin treatment resulted in a 57.9% reduction, when compared with placebo, in the risk of experiencing breakthrough overt hepatic encephalopathy during the course of this study.

Figure 3 Time to First Breakthrough Overt HE Episode (up to 6 Months of Treatment, Day 170) (ITT Population)



Sensitivity analyses

Because subjects who had ongoing comorbid conditions (i.e. known precipitating factors for hepatic encephalopathy episodes, including analgesic use, constipation, infection, and portal shunt surgery) at the time of randomization may have been unstable, a sensitivity analysis of the primary efficacy endpoint was carried out, where these subjects were excluded from the analysis. Rifaximin treatment resulted in significant reductions in the risk of breakthrough overt hepatic encephalopathy in subjects with or without comorbidities.

Because subjects who took concomitant medications, indicated for the treatment or prevention of hepatic encephalopathy, may have influenced the effect of rifaximin on the outcome of the primary endpoint, a second sensitivity analysis was performed whereby subjects satisfying the above condition were excluded from the ITT population. Rifaximin treatment resulted in a significant reduction in the risk of breakthrough overt hepatic encephalopathy; hazard ratio of rifaximin to placebo was 0.419 (95% CI: 0.275 to 0.640) ($p < 0.0001$).

Subgroup analyses

Subgroup analyses were conducted to determine the robustness and precision of the rifaximin treatment effect for the primary efficacy endpoint. Outcomes for the primary efficacy endpoint were evaluated in the following subgroups: geographic analysis region (North America versus Russia), sex, age (< 65 versus ≥ 65 years), race (white versus non-white), baseline MELD level (≤ 10 , 11 - 18, 19 - 24), baseline Conn score (0 versus 1), prior

lactulose use (yes versus no), diabetes at Baseline (yes versus no), duration of current verified remission (≤ 90 days versus > 90 days), and the number of hepatic encephalopathy episodes within the 6 months prior to randomization (2 versus > 2). The effect of rifaximin treatment in reducing the risk of experiencing breakthrough overt hepatic encephalopathy episodes during the 6-month treatment period was consistent across all subgroups.

Secondary efficacy endpoints

Results of “Time to first hepatic encephalopathy-related hospitalization”, “Changes from baseline in CLDQ fatigue domain score at end of treatment”, “Changes from baseline in venous ammonia levels at end of treatment”, “Changes from baseline in Conn scores” and “asterixis grades” were consistent with results of the primary efficacy endpoints.

Safety Results

The mean (\pm standard deviation) numbers of days of treatment with study drug were 130.3 (± 56.47) days in the rifaximin group and 105.7 (± 62.7) days in the placebo group. A total of 64 subjects (33 [rifaximin] and 31 [placebo]) received treatment for 141 to 168 days and 98 subjects (57 [rifaximin] and 41 [placebo]) received treatment for > 168 days.

The percentages of subjects who had treatment-emergent adverse events (TEAE), severe TEAEs, drug-related TEAEs, TEAEs resulting discontinuation, and who died were similar between placebo and rifaximin groups. A total of 79.9% of subjects (239 of 299) experienced TEAEs during the course of the study, including 80% of subjects (112 of 140) in the rifaximin group and 79.9% of subjects (127 of 159) in the placebo group. The most common TEAEs (ie, in $\geq 10\%$ of total subjects) were diarrhea (10.7% [rifaximin] versus 13.2% [placebo]), nausea (14.3% versus 13.2%), peripheral edema (15% versus 8.2%), fatigue (12.1% versus 11.3%), dizziness (12.9% versus 8.2%), ascites (11.4% versus 9.4%), and headache (10% versus 10.7%).

A total of 21 subjects died during the study, 11 subjects in the placebo group and 10 subjects in the rifaximin group. Deaths were predominantly due to conditions associated with disease progression, including hepatic cirrhosis, decompensated liver cirrhosis, hepatic failure, alcoholic cirrhosis, or end-stage liver failure (5 [rifaximin] and 5 [placebo]); and esophageal varices or esophageal varices hemorrhage (3 [rifaximin] and 2 [placebo]).

Supportive study (Protocol Number: RFHE3002)

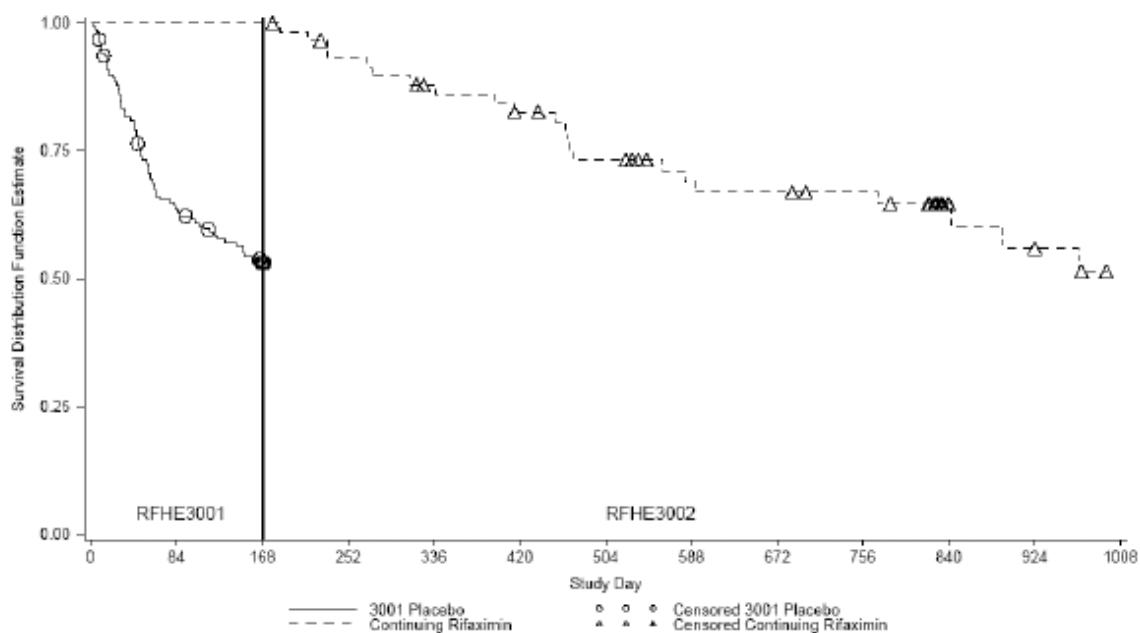
This study was a, multicenter, open-label, treatment-extension study evaluating the long-term safety and tolerability of rifaximin 550 mg bid in up to approximately 500 subjects with a history of hepatic encephalopathy. All eligible subjects had a history of hepatic encephalopathy, a Conn score of 0 to 2 at enrollment, and either successfully participated in a previous hepatic encephalopathy study with rifaximin (i.e. RFHE3001), or were new subjects enrolled with ≥ 1 verifiable episode of hepatic encephalopathy within 12 months prior to screening. Subjects who participated in RFHE3001 and experienced an HE episode or

associated symptoms were eligible for this study only if the investigator and subject did not perceive study medication as a possible cause of the hepatic encephalopathy episode or symptoms. Treatment in the RFHE3002 study was planned to continue for at least 24 months on an outpatient basis, or until regulatory approval of rifaximin for reduction in risk of overt hepatic encephalopathy recurrence, or until the sponsor closed the study, whichever came first.

Demographics

Most subjects had baseline Conn scores of either 0 (66%) or 1 (30%) and asterix grades of 0 (71%) or 1 (24%). The mean (standard deviation) duration of current verified remission from hepatic encephalopathy (time since most recent verified hepatic encephalopathy event) was substantially shorter in the new rifaximin group compared to the continuing rifaximin group. New and continuing subjects were also different with respect to the number of hepatic encephalopathy episodes experienced prior to screening for RFHE3002.

Figure 7 Kaplan Meier Estimates of Distribution of Time to First Breakthrough HE for Continuing Rifaximin Subjects Who Did Not Have an HE Episode in RFHE3001 versus Placebo



Unlike study RFHE3001, in which subjects were discontinued from the study after experiencing their first breakthrough overt hepatic encephalopathy episode, subjects had the option of continuing rifaximin therapy in study RFHE3002 after experiencing breakthrough overt hepatic encephalopathy. Therefore, it was possible to evaluate the incidence of breakthrough overt hepatic encephalopathy over time during rifaximin therapy. In the all rifaximin group, 42% of subjects (135 of 322) had one breakthrough overt hepatic encephalopathy episode during the course of the study. Of the 135 subjects with

breakthrough hepatic encephalopathy, most had 1 (64 subjects) or 2 (29 subjects) episodes. Forty-two subjects (13%) had 3 or more breakthrough hepatic encephalopathy episodes in RFHE3002.

While 30% of subjects had two hepatic encephalopathy episodes during the 6-month interval prior to the start of study RFHE3001, only 13% of subjects had two hepatic encephalopathy episodes during rifaximin therapy for up to 1260 days (median exposure = 513 days [1.4 years]) in study RFHE3002.

Overall, the proportion of subjects who had maintenance or improvement in Conn scores and in asterixis grades compared to baseline was high and similar between the new and continuing rifaximin groups.

Hospitalisation

A total of 200 subjects were hospitalized for any cause: 151 in the new rifaximin group, and 49 in the continuing rifaximin group. Normalizing for subject exposure (151/342.3 PEY), this represents a hospitalization rate of 0.44 event/PEY for the new rifaximin subjects. In the double-blind study RFHE3001, the all cause hospitalization rate was 0.92 event/PEY in the rifaximin group and 1.31 event/PEY in the placebo group.

A total of 109 subjects were hospitalized for breakthrough overt hepatic encephalopathy: 79 in the new rifaximin group and 18 in the continuing rifaximin group. Normalizing for subject exposure, this represents an hepatic encephalopathy hospitalization rate of 0.23 event/PEY for the new rifaximin group. In the double-blind study RFHE3001, the hepatic encephalopathy hospitalization rate was 0.38 event/PEY in the rifaximin group and 0.78 event/PEY in the placebo group.

Safety results

Treatment-emergent adverse events were most frequently reported (i.e. in 25% of all subjects) in the following System-Organ Classes: gastrointestinal disorders (67%); infections and infestations (57%); nervous system disorders (48%); general disorders and administration site conditions (45%); metabolism and nutrition disorders (41%); musculoskeletal and connective tissue disorders (35%); respiratory, thoracic and mediastinal disorders (35%); psychiatric disorders (31%); hepatobiliary disorders (30%); injury, poisoning and procedural complications (29%); skin and subcutaneous tissue disorders (29%); renal and urinary disorders (28%); blood and lymphatic system disorders (26%); and investigations (25%). The incidence of TEAEs by System-Organ Class was similar between the new rifaximin and the continuing rifaximin subjects.

The most common TEAEs (i.e. in 10% of total subjects) experienced by subjects were the following: hepatic encephalopathy (30%); urinary tract infection (23%); nausea (21%); peripheral edema (20%); anemia and ascites (16% each); abdominal pain, renal failure acute,

hypokalemia, and vomiting (14% each); dyspnea (13%); diarrhea, constipation, fatigue, muscle spasms, and depression (12% each); insomnia (11%); and cellulitis, pneumonia, dizziness (10% each). Note that signs and symptoms associated with hepatic encephalopathy were not considered adverse events unless they were more severe than expected for the subject's condition or met the definition of an serious adverse event.

Deaths

Table 21 Causes of Death for Subjects Who Died During Treatment or Within 30 Days After Last Dose of Study Medication

Cause of Death	RFHE3001		RFHE3002
	Rifaximin	Placebo	
Liver decompensation/failure	3	4	26
Cardiac	2	1	8
Hepatic neoplasms	0	2	8
Gastrointestinal hemorrhage/esophageal varices hemorrhage/ coagulation	3	2	6
Infection/pneumonia or lobar pneumonia	0	0	4
Renal failure	0	1	4
Infection/septic shock or sepsis	0	0	4
Respiratory failure	0	0	4
Multiorgan failure	0	0	1
Death (unknown cause)	0	0	1
Convulsion	0	0	1
Infection/urosepsis	0	1	0
Liver transplant rejection	1	0	0
Total	9	11	67

Assessor's overall conclusions

The single pivotal study supported by the open-label, long-term study provides adequate evidence for the use of Rifaximin in the treatment of hepatic encephalopathy. The number of patients with MELD scores >18 were less than 8%. Systemic exposure to Rifaximin increases with severity of liver impairment. Pharmacokinetics in renal impairment has not been studied.

The safety analyses show a high incidence of adverse effects in both the test and control arms. Considering the limited options available for the treatment of hepatic encephalopathy and the severe consequences of uncontrolled/ inadequately controlled hepatic encephalopathy, the safety profile can be considered acceptable.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

IV.2 Risk Management Plan

Ongoing safety concerns

Important identified risks

Cases of Clostridium Difficile Associated Diarrhoea (CDAD) have been reported with use of rifaximin with a range in severity from mild diarrhoea to fatal colitis. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out.

Allergic reactions (skin reactions and drug hypersensitivities of various nature and severity) are expected with rifaximin, despite the low systemic exposure after oral administration.

Important potential risks

Extensive clinical and post-marketing safety data confirms that rifaximin is well tolerated in a variety of indications and patient populations. The proposed indication does not create a new potential risk to the intended patient population that is not addressed by the proposed product labelling.

Summary of safety concerns and planned pharmacovigilance actions

Safety concern	Planned actions
1. Allergic reactions	Warnings included in SmPC: "Section 4.3 Contraindications" and PIL "Section 2 Before you take XIFAXANTA 500 mg film-coated tablets"
2. Potential for new drug-drug interactions	Warning in SmPC " <i>Section 4.5 Interaction with other medicinal products and other forms of interaction</i> ".
3. Potential off-label use: Rifaximin is proposed for the reduction in recurrence of episodes of hepatic encephalopathy (HE) in adults	Warnings in SmPC " <i>Section 4.4 Special warnings and precautions for use</i> " and PIL " <i>Section 1 What XIFAXANTA IS AND WHAT IT IS USED FOR</i> " and " <i>Section 2 Before you take XIFAXANTA</i> "
4. Potential off-label paediatric use: Rifaximin is proposed for the reduction in recurrence of episodes of hepatic encephalopathy (HE) in adults.	Warnings included in SmPC " <i>Section 4.2 Posology and method of administration</i> ".

Evaluation of the need for risk minimization activities

Safety concern	Routine risk minimization activities sufficient?	If yes, provide description of routine activity and justification
1. Allergic reactions	Yes	Appropriate labelling
2. Potential for new drug-drug interactions	Yes	Appropriate labelling.
3. Potential off-label paediatric use: Rifaximin is proposed for the reduction in recurrence of episodes of hepatic encephalopathy (HE) in adults	Yes	Appropriate labelling.

No risk minimisation measures beyond the product information are proposed with justification that this is not necessary due to:

- Extensive clinical and post-marketing experience with rifaximin
- No major hazard yet identified
- Safety data on drug utilization in studies with other indications/pathologies
- Clinical and post-marketing experience on long term treatments
- No evidence of potential overuse in post-marketing experience
- Product information (SmPC/PIL) sufficient at this stage, covering the limitations of current safety experience

From global post-marketing safety data analysis, there was no signal associated with prescription/medical errors or an increasing in errors of drug prescriptions. Therefore the potential for accidental medication errors by the patient is considered negligible.

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
<p>Allergic reactions</p>	<ul style="list-style-type: none"> Routine pharmacovigilance activities 	<p>SmPC: <i>Section 4.3</i> <i>Contraindications: Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients listed in section 6.1</i></p> <p>PIL <i>Section 2 What you need to know before you take TRADE NAME</i>: "Do not take TRADE NAME if: you are allergic (hypersensitive) to</p> <ul style="list-style-type: none"> rifaximin similar types of antibiotics (such as rifampicin or rifabutin) any of the other ingredients (listed in section 6)
<p><i>C. difficile</i> Associated Diarrhoea (CDAD)</p>	<ul style="list-style-type: none"> Routine pharmacovigilance activities Close monitoring of reports of reports of clostridial infections 	<ul style="list-style-type: none"> SmPC <i>Section 4.4 Special warnings and precautions for use: Clostridium difficile associated diarrhoea (CDAD)</i> has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out PIL <i>Section 2 What you need to know before you take TRADE NAME, Warnings and Precautions</i>: Treatment with any antibiotic including rifaximin may cause severe diarrhoea. This can happen several months after you have finished taking the medicine. If you have severe diarrhoea during or after using TRADE
		<p>NAME you should stop taking TRADENAME and contact your doctor immediately, and <i>Section 4 Possible side effects</i>: If you have severe diarrhoea during or after using this medicine. This may be due to an infection of the intestine</p> <ul style="list-style-type: none"> Continuous and close monitoring of safety signals deriving from PM data and periodical reporting to Health Authorities (PSUR)

<p>Potential for drug-drug interactions</p>	<ul style="list-style-type: none"> • Routine pharmacovigilance activities • Post-authorisation drug utilisation study (DUS) to evaluate the incidence of co-administration of rifaximin with other drugs 	<p><i>SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction:</i> “There is no experience regarding administration of rifaximin to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.</p> <p><i>In vitro</i> data show that rifaximin did not inhibit the major cytochrome P-450 (CYP) drug metabolizing enzymes (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In <i>in vitro</i> induction studies, rifaximin did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4.</p> <p>In healthy subjects, clinical drug interaction studies demonstrated that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics), due to the higher systemic exposure with respect to healthy subjects.</p> <p>An <i>in vitro</i> study suggested that rifaximin is a moderate substrate of P-glycoprotein(P-gp) and metabolized by CYP3A4. It is unknown whether concomitant drugs which inhibit P-gp and/or CYP3A4 can increase the systemic exposure of rifaximin.</p> <p>The potential for drug-drug interactions to occur at the level of transporter systems has been evaluated <i>in vitro</i> and these studies suggest that a clinical interaction between rifaximin and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MDR1, MRP2, MRP4, BCRP and BSEP)</p>
<p>Potential for cross-resistance to rifampicin</p>	<ul style="list-style-type: none"> • Routine pharmacovigilance activities 	<ul style="list-style-type: none"> • <i>SmPC Section 4.4</i> Special warnings and precautions for use “Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended.” • <i>SmPC Section 5.1</i> Pharmacodynamic properties Mechanism of resistance Experimental and clinical data suggest that the treatment with rifaximin of patients harbouring strains of <i>Mycobacterium tuberculosis</i> or <i>Neisseria meningitidis</i> will not select for rifampicin resistance.
<p>Potential off-label</p>	<ul style="list-style-type: none"> • Routine pharmacovigilance activities • Post-authorisation drug utilisation study (DUS) to assess indications for which rifaximin is prescribed and quantify any off-label use 	<ul style="list-style-type: none"> • Statement is included in the SmPC that rifaximin 550 mg is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age

Potential off-label paediatric use	<ul style="list-style-type: none"> Routine pharmacovigilance activities Post-authorisation drug utilisation study (DUS) to assess incidence of prescriptions in children 	<ul style="list-style-type: none"> SmPC: <i>Section 4.2 Posology and method of administration:</i> <i>Paediatric population:</i> “the safety and efficacy of TRADE NAME in paediatric patients (aged less than 18 years) have not been established”
Lack of data in the paediatric population	Monitoring of any report of use of rifaximin in children suffering from hepatic encephalopathy	
Lack of drug efficacy	<ul style="list-style-type: none"> Routine pharmacovigilance activities 	

IV.3 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended from a clinical viewpoint.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of TIXTELLER 550 mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

Satisfactory data from non-clinical studies have been provided. No new non-clinical concerns have been raised.

CLINICAL

The use of rifaximin for the reduction of recurrence of episodes of overt hepatic encephalopathy is supported by a well-conducted, placebo-controlled Phase III study, which demonstrated convincing evidence of reduced episodes in the rifaximin group compared to the placebo group. This primary endpoint was also supported by sensitivity analyses and sub group analyses. A long-term study for 24 months showed the efficacy was maintained over this duration.

The incidence of adverse events seen in the clinical trials was comparable to that in the placebo group. These have been mentioned under appropriate sections of the SmPC, as well as covered in the risk management plan.

There are limited effective options available for the treatment of hepatic encephalopathy. Rifaximin has been approved and used in a number of European countries and United States. Published literature also supports the use of rifaximin in hepatic encephalopathy.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with rifaximin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE -
SUMMARY**

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/ Justification for refuse
NL/H/4510 /IB/014/G	Addition site for Primary packaging - Secondary packaging - Batch control, for microbiological testing only - Batch release Microbiological testing, change from membrane filtration to plate-count method	--	3-8-2019	Approval	--