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Artwork Approval Signature

Regulatory _____

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CODICE CARTELLINA	DATA MODIFICA IMPIANTO	CORPO	FONTS
C. 00987/2	26/09/2017	**TESTO: 8** **INTERLINEA: 9**	**Futura / Myriad pro**

ARTICOLO	PRODOTTO
Prospetto	**XIFAXAN 550 mg - SINGAPORE**

☐ **Steso** ■ **Piegato** ☐ **Bobina** ☐ **Booklet**

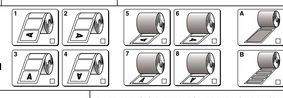
■ **Con microforatura** ☐ **Senza microforatura**

GRAMMATURA CARTA	FORMATO	LAYOUT DI RIFERIMENTO	% DI COPERTURA TESTI/SUPERFICIE	SCALA
40 g	**165 X 560/280**		**100 %**	**1:1**

CODICE ALFASIGMA	CODICE CLIENTE	RIF. PRATICA
43000871		

SENSO DI SVOLGIMENTO N.

SOLO PER PROSPETTI IN BOBINA



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1	2	3	4

Edizione	Data allestimento
0	**04.09.2017**

RIF. LAETUS **1498 SLLLSLLSLL**

MASTER DI RIFERIMENTO

NOTE / RIF. IMPIANTO PRECEDENTE
01251969

VISTO SI STAMPI

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Xifaxan 550 mg film-coated tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
XIFAXAN 550 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 550 mg rifaximin.
Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Pink, oval biconvex 10 mm x 19 mm film-coated tablets embossed with "RX" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
XIFAXAN is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age (see section 5.1).
In the pivotal study, 91% of the patients were using concomitant lactulose.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
Recommended dose: 550 mg twice a day. The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction (see sections 4.4, 5.1 and 5.2).
XIFAXAN can be administered with or without food.
Paediatric population
The safety and efficacy of XIFAXAN in paediatric patients (aged less than 18 years) have not been established.
Elderly
No dosage adjustment is necessary as the safety and efficacy data of XIFAXAN showed no differences between the elderly and the younger patients.
Hepatic impairment
No dosage adjustment is necessary for patients with hepatic insufficiency (see section 4.4).
Renal impairment
Although dosing change is not anticipated, caution should be used in patients with impaired renal function (see section 5.2).
Method of administration
Orally with a glass of water.

4.3 Contraindications
- Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients listed in section 6.1.
- Cases of intestinal obstruction.

4.4 Special warnings and precautions for use
Clostridium difficile associated diarrhoea (CDAD) 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.
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.
Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine.
Hepatic Impairment: use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 (see section 5.2).
Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. However, such interactions have not been commonly reported. It is recommended to take additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50 µg (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
There is no experience regarding administration of rifaximin to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.
In vitro 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 *in vitro* induction studies, rifaximin did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4.
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.
An *in vitro* 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.
The potential for drug-drug interactions to occur at the level of transporter systems has been evaluated *in vitro* 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).

4.6 Fertility, pregnancy and lactation
Pregnancy
There is no or limited data from the use of rifaximin in pregnant women.
Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3).
As a precautionary measure, use of rifaximin during pregnancy is not recommended.
Breastfeeding
It is unknown whether rifaximin/metabolites are excreted in human milk.
A risk to the breast-fed child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility.

4.7 Effects on ability to drive and use machines
Dizziness has been reported in clinical controlled trials. However, rifaximin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Clinical Trials:
The safety of rifaximin in patients in remission from hepatic encephalopathy (HE) was evaluated in two studies, a randomised, double-blind, placebo-controlled phase 3 study RFHE3001 and a long-term, open-label study RFHE3002.
Study RFHE3001 compared 140 patients treated with rifaximin (dose of 550 mg twice daily for 6 months) to 159 patients treated with placebo, while study RFHE3002 treated 322 patients, of whom 152 from the RFHE3001 study, with rifaximin 550 mg twice daily for 12 months (66% of patients) and for 24 months (39% of patients), for a median exposition of 512.5 days.
In addition, in three supportive studies 152 HE patients were treated with varying doses of rifaximin from 600 mg to 2400 mg per day for up to 14 days.
All adverse reactions that occurred in patients treated with rifaximin at an incidence ≥ 5% and at a higher incidence (≥1%) than placebo patients in RFHE3001 are reported in the following table.

Table 1: Adverse reactions occurring in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo in RFHE3001

MedDRA System Organ Class	**Event**	**Placebo N=159**		**Rifaximin N= 140**	
		n	**%**	**n**	**%**
Blood and lymphatic system disorders	Anaemia	6	3.8	11	7.9
Gastrointestinal disorders	Ascites	15	9.4	16	11.4
	Nausea	21	13.2	20	14.3
	Abdominal pain upper	8	5.0	9	6.4
General disorders and administration site conditions	Oedema peripheral	13	8.2	21	15.0
	Pyrexia	5	3.1	9	6.4
Musculoskeletal and connective tissue disorders	Muscle spasms	11	6.9	13	9.3
	Arthralgia	4	2.5	9	6.4
Nervous system disorders	Dizziness	13	8.2	18	12.9
Psychiatric disorders	Depression	8	5.0	10	7.1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7	4.4	9	6.4
Skin and subcutaneous tissue disorders	Pruritus	10	6.3	13	9.3
	Rash	6	3.8	7	5.0

Table 2 includes adverse reactions observed in the placebo-controlled study RFHE3001 and long term study RFHE3002, listed by MedDRA system organ class and frequency category.
Frequency categories are defined using the following convention:
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions listed by MedDRA system organ class and frequency category.

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Clostridial infection, urinary tract infection, candidiasis	Pneumonia, cellulitis, upper respiratory tract infections, rhinitis	
Blood and lymphatic system disorders		Anaemia		Thrombocytopenia
Metabolism and nutrition disorders		Anorexia, hyperkalaemia	Dehydration	
Psychiatric disorders	Depression	Confusional state, anxiety, hypersomnia, insomnia		
Nervous system disorders	Dizziness, headache	Balance disorders amnesia, convulsion, attention disorders hypoesthesia, memory impairment		Anaphylactic reactions, angioedemas, hypersensitivity
Vascular disorders		Hot flush	Hypertension, hypotension	Presyncope, syncope
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Pleural effusion	Chronic obstructive pulmonary disease	
Gastrointestinal disorders	Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites	Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort	Constipation	
Hepatobiliary disorders				Liver function tests abnormalities
Skin and subcutaneous tissue disorders	Rashes, pruritus			Dermatitis, eczema

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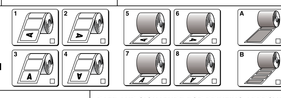

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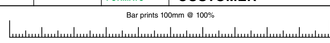

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MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Musculoskeletal and connective tissue disorders	Muscle spasms, arthralgia	Myalgia	Back pain	
Renal and urinary disorders		Dysuria, pollakiuria	Proteinuria	
General disorders and administration site conditions	Oedema peripheral	Oedema, pyrexia	Asthenia	
Investigations				International normalised ratio abnormalities
Injury, poisoning and procedural complications		Fall	Contusions, procedural pain	

4.9 Overdose
No case of overdose has been reported.
In clinical trials with patients suffering from traveller's diarrhoea doses of up to 1800 mg/day have been tolerated without any severe clinical sign. Even in patients/subjects with normal bacterial flora rifaximin in dosages of up to 2400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage.
In case of accidental overdose, symptomatic treatment and supportive care are suggested.

5. PHARMACOLOGICAL PROPERTIES
XIFAXAN contains rifaximin (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: intestinal, anti-infective - antibiotics - ATC code: A07AA11.
Mechanism of action
Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis.
Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. 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.
Mechanism of resistance
The development of resistance to rifaximin is primarily a reversible chromosomal one-step alteration in the *rpoB* gene encoding the bacterial RNA polymerase.
Clinical studies that investigated changes in the susceptibility of intestinal flora of patients affected by traveller's diarrhoea failed to detect the emergence of drug resistant Gram-positive (e.g. *enterococci*) and Gram-negative (*E. coli*) organisms during a three-day course of treatment with rifaximin.
Development of resistance in the normal intestinal bacterial flora was investigated with repeated, high doses of rifaximin in healthy volunteers and Inflammatory Bowel Disease patients. Strains resistant to rifaximin developed, but were unstable and did not colonise the gastrointestinal tract or replace rifaximin-sensitive strains. When treatment was discontinued resistant strains disappeared rapidly.
Experimental and clinical data suggest that the treatment with rifaximin of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitidis* will not select for rifampicin resistance.
Susceptibility
Rifaximin is a non-absorbed antibacterial agent. *In vitro* susceptibility testing cannot be used to reliably establish susceptibility or resistance of bacteria to rifaximin. There are currently insufficient data available to support the setting of a clinical breakpoint for susceptibility testing.
Rifaximin has been evaluated *in vitro* on several pathogens including ammonia producing bacteria as *Escherichia coli* spp, *Clostridium* spp, *Enterobacteriaceae*, *Bacteroides* spp. Due to the very low absorption from the gastro-intestinal tract rifaximin is not clinically effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.
Clinical efficacy
The efficacy and safety of rifaximin 550 mg twice daily in adult patients in remission from HE was evaluated in a phase 3 pivotal, 6-month, randomised, double-blind, placebo-controlled study RFHE3001.
Two-hundred ninety-nine subjects were randomised to treatment with rifaximin 550 mg twice daily (n=140) or placebo (n= 159) for 6 months. More than 90% of the subjects in both groups received concomitant lactulose. No patients were enrolled with a MELD score > 25.
The primary endpoint was the time to first breakthrough overt HE episode and patients were withdrawn after a breakthrough overt HE episode. Thirty-one of 140 subjects (22%) of rifaximin group and 73 of 159 (46%) subjects of placebo group experienced a breakthrough overt HE episode during the 6-month period. Rifaximin reduced the risk of HE breakthrough by 58% (p< 0.0001) and the risk of HE-related hospitalizations by 50% (p< 0.013), compared with placebo.
The longer-term safety and tolerability of rifaximin 550 mg twice daily administered for at least 24 months was evaluated in 322 subjects in remission from HE in study RFHE3002. One hundred fifty-two subjects rolled over from RFHE3001 (70 from the rifaximin group and 82 from the placebo), and 170 subjects were new. Eighty-eight percent of patients were administered concomitant lactulose.
Treatment with rifaximin for periods up to 24 months (OLE study RFHE3002) did not result in any loss of effect regarding the protection from breakthrough overt HE episodes and the reduction of the burden of hospitalization. Time to first breakthrough overt HE episode analysis showed long-term maintenance of remission in both groups of patients, new and continuing rifaximin.

5.2 Pharmacokinetic properties
Absorption
Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (Inflammatory Bowel Disease), plasma levels are negligible (less than 10 ng/mL). In HE patients, administration of rifaximin 550 mg twice a day showed mean rifaximin exposure approximately 12-fold higher than that observed in healthy volunteers following the same dosing regimen. A clinically irrelevant increase of rifaximin systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.
Distribution
Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when rifaximin 550 mg was administered.
Biotransformation
Analysis of faecal extracts demonstrated that rifaximin is found as the intact molecule, implying that it is neither degraded nor metabolised during its passage through the gastrointestinal tract.
In a study using radio-labelled rifaximin, urinary recovery of rifaximin was 0.025% of the administered dose, while <0.01% of the dose was recovered as 25-desacetylrifaximin, the only rifaximin metabolite that has been identified in humans.
Elimination
A study with radio-labelled rifaximin suggested that ^{14}C-rifaximin is almost exclusively and completely excreted in faeces (96.9 % of the administered dose). The urinary recovery of ^{14}C-rifaximin does not exceed 0.4% of the administered dose.
Linearity/non-linearity
The rate and extent of systemic exposure of humans to rifaximin appeared to be characterized by non-linear (dose-dependent) kinetic which is consistent with the possibility of dissolution-rate-limited absorption of rifaximin.
Special Populations
Renal impairment
No clinical data are available on the use of rifaximin in patients with impaired renal function.
Hepatic impairment
Clinical data available for patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers.
The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis.
Therefore no dosage adjustment is recommended because rifaximin is acting locally.
Paediatric population
The pharmacokinetics of rifaximin has not been studied in paediatric patients of any age. Population studied in both the reduction in recurrence of hepatic encephalopathy (HE) and in the acute treatment of HE included patients aged ≥ 18 years.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In a rat embryofetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300 mg/kg/day (2.7 times the proposed clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed (at doses similar to those proposed clinically for hepatic encephalopathy). The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Sodium starch glycolate type A
Glycerol distearate
Colloidal anhydrous silica
Talc
Microcrystalline cellulose
Film coat (opadry oy-s-34907):
Hypromellose
Titanium dioxide (E171)
Disodium edetate
Propylene glycol
Red iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30 °C.

6.5 Nature and contents of container
PVC-PE-PVDC/Aluminium foil blisters in cartons of 14, 28, 42, 56 or 98 tablets.
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Alfasigma S.p.A. - Via Enrico Fermi, 1 - 65020 Alanno (PE), Italy

8. DATE OF REVISION OF THE TEXT
October 2017

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