RIFAXEROSE

(Rifaximin 550 mg) Film coated tablets

Clinical particulars

Therapeutic indications

Rifaxerose is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age . used as primary prophylaxis of hepatic encephalopathy

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.

Used in traveler's Diarrhea .

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 .

Rifaxerose can be administered with or without food.

Paediatric population

The safety and efficacy of Rifaxerose 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 Rifaxerose showed no differences between the elderly and the younger patients.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic insufficiency .

Renal impairment

Although dosing change is not anticipated, caution should be used in patients with impaired renal function .

Method of administration

Orally with a glass of water.

Contraindications

- Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients .
- Cases of intestinal obstruction.

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: Not used in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 .

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 .

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).

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 .
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.

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.

Undesirable effects

Table 1: Adverse reactions occurring in patients receiving rifaximin

MedDRA System Organ Class	Event
Blood and lymphatic system disorders	Anaemia
Gastrointestinal disorders	Ascites
	Nausea
	Abdominal pain upper
General disorders and administration site conditions	Oedema peripheral
	Pyrexia
Musculoskeletal and connective tissue disorders	Muscle spasms
	Arthralgia
Nervous system disorders	Dizziness
Psychiatric disorders	Depression
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Skin and subcutaneous tissue disorders	Pruritus
	Rash

Table 2 includes adverse reactions 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.

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
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	

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.

Pharmacological properties

Pharmacodynamics properties

Pharmacotherapeutic group: intestinal, anti-infective - antibiotics

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*.

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.

Inactive ingredient: Microcrystalline cellulose (Avicel pH 102), glyceryl behenate ,sodium starch glycolate ,colloidal silicon dioxide(Aerosil 200) , Hyperomellose (Methocel E5), triacetin, Talc powder, Titanium dioxide, ferric oxide red C.I.N.47005, Edeta disodium.

12 HOW SUPPLIED/STORAGE AND HANDLING

Carton box contains 1 (Hard AL/ white opaque PVC) blister of 10 film coated tablets and inner bilingual leaflets.

Storage

Store RIFAXEROSE Tablets at temperature not exceeding 30°C

(THIS IS A MEDICAMENT)

-Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-Do not by yourself interrupt the period of treatment prescribed.
-Do not repeat the same prescription without consulting your doctor.

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