1.17 Summary of Product Characteristics (SPC)

1.17.1 Product information for Health Professionals

(For All Products subject to Medical Prescription)

1. Name of the medicinal Product

Rifaximin Tablets 550 mg

2. Qualitative and quantitative composition

Each film coated tablet contains:

Rifaximin BP 550 mg

Excipients Q.S.

Color: Sunset Yellow Lake

Composition of the product:

Sr. No.	Ingredients Chemical Name	Specification	Quantity per tablet (mg)	Function
1	Rifaximin	BP	550.00	Active
2	Maize Starch	BP	90.63	Diluent
3	Microcrystalline Cellulose	BP	8.00	Diluent
4	Croscarmellose Sodium	BP	18.66	Disintegrant
5	Tween 80	BP	14.66	Non-ionic surfactant
6	Crospovidone	BP	18.66	Binder
7	Sodium Methyl Hydroxybenzoate	BP	0.47	Antimicrobial preservative
8	Sodium Propyl Hydroxybenzoate	BP	0.24	Antimicrobial preservative
9	Purified Talc	BP	9.30	Glidant
10	Magnesium Stearate	BP	9.30	Lubricant
11	Colloidal Silicon Dioxide-200	BP	4.70	Glidant
12	Sodium Lauryl Sulphate	BP	44.00	Lubricant
13	Povidone K-30	BP	14.66	Binder
14	Dr. Coat	IHS	15.60	Coating agent
15	Isopropyl Alcohol	BP	0.10 ml	Solvent
16	Dichloromethane	BP	0.15 ml	Solvent
17	Colour: Sunset Yellow Lake	IHS	1.12	Coloring Agent
Total Average Weight of Tablets			**800.00 mg**	

BP: British Pharmacopoeia

IHS: In-House Specification

3. Pharmaceutical form

Solid oral dosage form, Tablets

4. Clinical particulars

4.1 Therapeutic indications

Rifaximin Tablets 550 mg is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

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.

Rifaximin Tablets 550 mg can be administered with or without food.

Paediatric population

The safety and efficacy of Rifaximin Tablets 550 mg 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 Rifaximin Tablets 550 mg 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.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients which is used in formulation.

• 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.

Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein such as ciclosporin is needed.

Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with rifaximin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

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, oral contraceptives), due to the higher systemic exposure with respect to healthy subjects.

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.

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

Following table includes adverse reactions observed in the placebo-controlled study RFHE3001, long term study RFHE3002 and from post-marketing experience, listed by MedDRA system organ class and frequency category.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table: 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
Immune system disorders				Anaphylactic reactions, angioedemas, hypersensitivity
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		
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	

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal, anti-infective - antibiotics

ATC code: D06AX11

Pharmacodynamic effects

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.

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.

5.3 Pre-clinical 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.

6.1 List of excipient

- Maize Starch BP
- Microcrystalline Cellulose BP
- Calcium Sulfate Dihydrate BP
- Croscarmellose Sodium BP
- Crospovidone BP
- Povidone K 30 BP
- Isopropyl Alcohol BP
- Purified Talc BP
- Magnesium Stearate BP
- Sodium Starch Glycolate BP
- Dr. Coat IHS
- Isopropyl Alcohol BP
- Dichloromethane BP
- Colour: Sunset Yellow Lake IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

An orange colored, elongated shape, biconvex, film coated tablet having a break line on one side of each tablet. Such 10 tablets are packed in alu-alu blister. Such 1 Alu-Alu blister is packed in a printed carton along with insert.

6.6 Special precautions for disposal <and other handling>

Not Applicable

7. Marketing Authorization Holder:

SANJEEVANI BIO-TECH EXIM PVT. LTD.

8. Marketing Authorization Number:

Not applicable.

9. Date of first Authorization /renewal of the authorization:

Not applicable.

10. Date of revision of text:

Not applicable.