Rifaxol Tablet
(R i f a x i m i n)

ریفیکزول ٹیبلٹ
(ریفیکزِمن)

COMPOSITION
Rifaxol Tablet 200mg
Each film coated tablet contains:
Rifaximin 200mg
(BP specifications)
Rifaxol Tablet 550mg
Each film coated tablet contains:
Rifaximin 550mg
(BP specifications)

DESCRIPTION
Rifaxol (Rifaximin), a non-aminoglycoside semi-synthetic, non-systemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin.

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.

INDICATIONS
To reduce the development of drug-resistant bacteria and maintain the effectiveness of RIFAXIMIN and other antibacterial drugs, RIFAXIMIN when used to treat infection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Travelers' Diarrhea
RIFAXIMIN is indicated for the treatment of travelers' diarrhea (TD) caused by non-invasive strains of Escherichia coli in adults and pediatric patients 12 years of age and older.

Limitations of Use
RIFAXIMIN should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli.

Hepatic Encephalopathy
RIFAXIMIN is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.

Irritable Bowel Syndrome with Diarrhea
RIFAXIMIN is indicated for the treatment of irritable bowel
RIFAXIMIN is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

DOSAGE & ADMINISTRATION

Travelers' Diarrhea
The recommended dose of RIFAXIMIN is one 200 mg tablet taken orally three times a day for 3 days.

Hepatic Encephalopathy
The recommended dose of RIFAXIMIN is one 550 mg tablet taken orally two times a day.

Irritable Bowel Syndrome with Diarrhea
The recommended dose of RIFAXIMIN is one 550 mg tablet taken orally three times a day for 14 days.
Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.
RIFAXIMIN can be taken with or without food.

PHARMACODYNAMICS
Rifaximin is a structural analog of rifampin and a non-systemic, gastrointestinal site-specific antibiotic. This non-systemic property of the drug is due to the addition of a pyridoimidazole ring, which renders it non-absorbable. Rifaximin acts by inhibiting bacterial ribonucleic acid (RNA) synthesis and contributes to restore intestinal microflora imbalance. Other studies have also shown rifaximin to be a pregnane X receptor (PXR) activator. As PXR is responsible for inhibiting the pro-inflammatory transcription factor NF-kappa B (NF-κB) and is inhibited in inflammatory bowel disease (IBD), rifaximin was proven to be effective for the treatment of IBS-D.

PHARMACOKINETICS

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 14C-rifaximin is almost exclusively and completely excreted in faeces (96.9 % of the administered dose). The urinary recovery of 14C-rifaximin does not exceed 0.4% of the administered dose.

WARNINGS AND PRECAUTIONS
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 discoloration 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 cyclosporine 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.

SIDE EFFECTS

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, angioedema, hypersensitivity.

Metabolism and nutrition disorders

Anorexia, hyperkalemia, 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, esophageal 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

Edema peripheral, edema, pyrexia, asthenia.

Investigations

International normalised ratio abnormalities.

Injury, poisoning and procedural complications

Fall, Contusions, procedural pain.

DRUG INTERACTIONS

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.

Both decreases and increases in international normalized ratio 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 rifaximin. Adjustments in the dose of oral anticoagulants may be necessary.

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.

In healthy subjects, co-administration of a single dose of cyclosporine (600 mg), a potent P-glycoprotein inhibitor, with a single dose of rifaximin (550 mg) resulted in 83-fold and 124-fold increases in rifaximin mean Cmax and AUC∞.

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 (MRP2, MRP4, BCRP and BSEP).

OVERDOSE

No case of overdose has been reported.

In clinical trials with patients suffering from travellers' 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.

CONTRAINDICATIONS

Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

Cases of intestinal obstruction.

STORAGE & INSTRUCTIONS:

Store between 15-25°C. Protect from heat, sunlight and moisture. Keep away from the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

Rifaxol Tablet 200mg
10 Tablets

Rifaxol Tablet 550mg
10 Tablets

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف معتمد ڈاکٹر کے نسخہ کے مطابق فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
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Lahore, Pakistan.