

**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

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**TORFIX 400/550**  
(Rifaximin Tablets 400 mg/550 mg)

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**COMPOSITION**

TORFIX 400

Each film coated tablet contains:

Rifaximin Ph.Eur .....400 mg

Colour: Sunset yellow FCF & Titanium Dioxide I.P.

TORFIX 550

Each film coated tablet contains:

Rifaximin Ph. Eur.....550 mg

Colours: Sunset Yellow FCF & Titanium Dioxide I.P.

**DOSAGE FORM**

Film coated tablet

**INDICATION**

TORFIX 400 is indicated for the treatment of hepatic encephalopathy.

TORFIX 550 is indicated for reduction in risk of Overt Hepatic Encephalopathy (HE) recurrence in patients  $\geq$  18 years of age.

**DOSE AND METHOD OF ADMINISTRATION**

Recommended dose: 400 mg thrice a day or 550 mg twice a day. The clinical benefit was established from a reported 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 can be administered with or without food.

***Paediatric population***

The safety and efficacy of rifaximin 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 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.

### **USE IN SPECIAL POPULATIONS**

#### 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.

### **CONTRAINDICATIONS**

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

### **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 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.

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.

## **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), 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).

## **UNDESIRABLE EFFECTS**

### Clinical Trials:

The safety of rifaximin in patients in remission from hepatic encephalopathy (HE) was evaluated in two reported 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 RFHE 3001 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  $\geq 5\%$  and at a higher incidence ( $\geq 1\%$ ) than placebo patients in RFHE3001 are reported in the following table.

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

| MedDRA System Organ Class                                   | Event                | Placebo<br>N=159 |      | Rifaximin<br>N= 140 |      |
|---|----------------------|------------------|------|---------------------|------|
|   |                      |                  |      |                     |      |
| <b>Blood and lymphatic system Disorders</b>                 | Anaemia              | 6                | 3.8  | 11                  | 7.9  |
| <b>Gastrointestinal disorders</b>                           | Ascites              | 15               | 9.4  | 16                  | 11.4 |
|   | Nausea               | 21               | 13.2 | 20                  | 14.3 |
|   | Abdominal pain upper | 8                | 5.0  | 9                   | 6.4  |
| <b>General disorders and administration site conditions</b> | Oedema peripheral    | 13               | 8.2  | 21                  | 15.0 |
|   | Pyrexia              | 5                | 3.1  | 9                   | 6.4  |
| <b>Musculoskeletal and connectivetissue disorders</b>       | Muscle spasms        | 11               | 6.9  | 13                  | 9.3  |
|   | Arthralgia           | 4                | 2.5  | 9                   | 6.4  |
| <b>Nervous system disorders</b>                             | Dizziness            | 13               | 8.2  | 18                  | 12.9 |
| <b>Psychiatric disorders</b>                                | Depression           | 8                | 5.0  | 10                  | 7.1  |
| <b>Respiratory, thoracic andmediastinal disorders</b>       | Dyspnoea             | 7                | 4.4  | 9                   | 6.4  |
| <b>Skin and subcutaneous tissue disorders</b>               | 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 studyRFHE3002, listed by MedDRA system organ class and frequency category.

Frequency categories are defined using the following convention:

Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  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        |
|---|------------|---|---|------------------|
| <b>Infections and infestations</b>          |            | Clostridial infection, urinary tract infection, candidiasis | Pneumonia, cellulitis, upper respiratory tract infections, rhinitis |                  |
| <b>Blood and lymphatic system disorders</b> |            | Anaemia   |   | Thrombocytopenia |
| <b>Metabolism and nutrition disorders</b>   |            | Anorexia, hyperkalaemia                                     | Dehydration   |                  |
| <b>Psychiatric disorders</b>                | Depression | Confusional state,  |   |                  |

|   |   |   |  |  |
|---|---|---|--|--|
|   |   | anxiety,<br>hypersomnia,<br>insomnia  |  |  |
| <b>Nervous system disorders</b>                             | Dizziness,<br>headache  | Balance disorders<br>amnesia,<br>convulsion,<br>attention disorders<br>hypoesthesia,<br>memory impairment |  | Anaphylactic<br>reactions,<br>angioedemas,<br>hypersensitivity |
| <b>Vascular disorders</b>                                   |   | Hot flush   | Hypertension,<br>hypotension             | Presyncope,<br>syncope   |
| <b>Respiratory, thoracic, and mediastinal disorders</b>     | Dyspnoea  | Pleural effusion  | Chronic obstructive<br>pulmonary disease |  |
| <b>Gastrointestinal disorders</b>                           | Abdominal<br>pain upper,<br>abdominal<br>distension,<br>diarrhoea,<br>nausea,<br>vomiting,<br>ascites | Abdominal pain,<br>oesophageal varices<br>haemorrhage, dry<br>mouth, stomach<br>discomfort                | Constipation                             |  |
| <b>Hepatobiliary disorders</b>                              |   |   |  | Liver function<br>tests abnormalities                          |
| <b>Skin and subcutaneous tissue disorders</b>               | Rashes,<br>pruritus   |   |  | Dermatitis,<br>eczema  |
| <b>Musculoskeletal and connective tissue disorders</b>      | Muscle<br>spasms,<br>arthralgia   | Myalgia   | Back pain                                |  |
| <b>Renal and urinary disorders</b>                          |   | Dysuria, pollakiuria  | Proteinuria,                             |  |
| <b>General disorders and administration site conditions</b> | Oedema<br>peripheral  | Oedema, pyrexia   | Asthenia                                 |  |
| <b>Investigations</b>                                       |   |   |  | International<br>normalised ratio<br>abnormalities             |
| <b>Injury, poisoning and procedural complications</b>       |   | Fall  | Contusions,<br>procedural pain           |  |

**Overdose**

No case of overdose has been reported.

In reported 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.

## **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**

Rifaximin is (4-desoxy-4-methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form  $\alpha$ .

### **Pharmacodynamic 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*.

### 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 reported 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 break through 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.

### **Pharmacokinetic properties**

#### **Absorption**

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph  $\alpha$  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 <sup>14</sup>C-rifaximin is almost exclusively and completely excreted in faeces (96.9 % of the administered dose). The urinary recovery of <sup>14</sup>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  $\geq 18$  years.



**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 embryo fetal 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.

**EXPIRY DATE**

Do not use later than the date of expiry.

**PACKAGING INFORMATION**

Torfix 400 is available as strip of 10 tablets.

Torfix 550 is available as strip of 10 tablets.

**STORAGE AND HANDLING INSTRUCTIONS**

Store in a dry place at a temperature not exceeding 25°C. Keep out of reach of children.

**MARKETED BY**

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**IN/TORFIX/400,550mg/Mar-2015/01/PI**