SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COLIDUR FORT 550 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Rifaximin 550 mg

Excipients:

Sodium starch glycolate 20.41 mg

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film tablet

Pink, notched, oval shaped film-coated tablets.

4. CLINICAL PROPERTIES

4.1 Therapeutic indications

- Reducing the recurrence of overt hepatic encephalopathy episodes in patients 18 years of age and older,
- It is indicated for the treatment of diarrhea-predominant irritable bowel syndrome.

4.2 Posology and method of administration

Posology / Application frequency and duration:

Depending on the doctor's recommendation, the amount and frequency of doses can be changed.

Recommended dosage:

COLIDUR FORT is used twice a day. Clinical benefit results from treatment with the drug for 6 months. Treatment beyond 6 months of therapy should consider the balance of individual benefits and risks associated with progression of hepatic dysfunction.

COLIDUR FORT is used three times a day for 14 days in diarrhea-predominant irritable bowel syndrome. Patients with recurrent symptoms may be re-treated with the same dosing regimen twice.

Additional information on special populations:

Kidney failure:

There are no clinical data on the administration of rifaximin in patients with renal impairment.

Liver failure:

Due to the limited systemic absorption of rifaximin, no dose adjustment is recommended in patients with hepatic impairment.

Pediatric population:

The efficacy and safety of the drug has not been proven in children under 18 years of age.

Geriatric population:

Since it does not differ in efficacy and safety between elderly and young patients; There is no need to apply different dosages in the elderly.

4.3 Contraindications

It should not be used in case of hypersensitivity to rifaximin, other rifamycins or any of the excipients (see Section 6.1).

It should not be used in patients with even partial intestinal obstruction or severe intestinal ulceration lesions.

4.4 Special warnings and precautions for use

Clostridium difficile associated diarrhea:

Clostridium difficile associated diarrhea (CDAD) has been reported with almost all antibacterial drugs, including rifaximin. Treatment with antibacterial agents causes changes in the normal flora of the colon resulting from overgrowth of *C. difficile*. A potential association between CDAD and pseudomembranous colitis (PMC) and rifaximin treatment cannot be excluded. *C. difficile* produces toxins A and B that

contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* increase morbidity and mortality, and these infections may be resistant to antimicrobial therapy and may require colectomy. CDAD should be considered in all patients who develop diarrhea following antibiotic use. If CDAD has occurred two months after use of the antibacterial agent, careful medical history should be taken. If CDAD is suspected or CDAD has been confirmed; Antibiotics that are not used directly against *C. difficile* but continue to be used may need to be discontinued. In such a case, appropriate fluid and electrolyte support, protein support, antibiotic therapy and surgical evaluation should be performed for the treatment of CDAD, as indicated in the clinic. *Candida albicans* is one of the pathogens causing the development of antibiotic-associated diarrhea and *Candida albicans* was isolated from the faecal specimens of 20% of patients given 1200 mg of rifaximin daily.

Development of drug-resistant bacteria:

Possible infection and induction of bacterial resistance should be considered during treatment with rifaximin, especially when long-term therapy is considered. In a comparative study with placebo, no cases were observed in the placebo group following 6 months of rifaximin treatment, whereas 2 cases of *Clostridium difficile* (*C. difficile*) infection were observed in the rifaximin group, although it was effective against this bacterium.

Although it is believed that the selection of resistant mutants of gram-negative and gram-positive bacteria will be very low under anaerobic conditions in the gastrointestinal tract, it cannot be excluded that this will not occur. Therefore, caution should be exercised in patients, especially when considering long-term rifaximin therapy. In cases where bacterial resistance developed after short-term (5 days) treatment with rifaximin, it was observed that these resistant bacteria disappeared rapidly after treatment was stopped, but such data were not available for long-term treatments. In anaerobic bacteria, especially gram negative bacilli, re-sensitivity to rifaximin takes longer time than anaerobic species.

Severe (Child_Pugh C) liver failure:

Rifaximin has been shown to be safe in healthy volunteers. However, liver cirrhosis significantly affects the pharmacokinetics of this drug. Systemic exposure is increased in patients with severe hepatic impairment. Compared with the control group; The plasma drug concentration in patients with liver cirrhosis increased by up to tenfold. Increased systemic exposure observed in patients with severe hepatic impairment; not seen in animal toxicology studies. Clinical trials are limited for patients with a MELD (Model for End-Stage Liver Disease) score <25. Therefore, COLIDUR FORT should be used with caution in patients with severe hepatic impairment (Child-Pugh C) and a MELD score >25.

Electrolyte irregularities:

Significant increases in serum sodium and potassium concentrations have been reported during treatment with rifaximin. In cirrhotic patients in whom electrolyte disturbances are associated with the development of hepatic encephalopathy, care and precautions should be taken for such changes.

Vitamin K synthesis:

A remarkable reduction in fecal Escherichia coli counts has been demonstrated with treatment with rifaximin at a daily dose of 800 mg for five days. Since this bacterium is important for vitamin K synthesis, the already impaired coagulation status in patients with cirrhosis may be further impaired by long-term rifaximin therapy.

Concomitant use with other rifampicin derivatives:

Concomitant use of rifaximin with other rifampicins is not recommended due to insufficient available data and the potential to cause unknown consequences with severe disruption of the intestinal flora.

Concomitant use with estrogen-containing oral contraceptives:

Although not frequently reported, the efficacy of oral estrogenic contraceptives may decrease after the use of rifaximin due to its effect on the intestinal flora. If an oral contraceptive with an estrogen content of less than 50 µg is to be used, an additional contraceptive precaution is recommended.

Concomitant use with P-Glycoprotein inhibitors:

Concomitant use of rifaximin with P-Glycoprotein inhibitors significantly increases systemic exposure to rifaximin. Caution should be exercised in the concomitant use of rifaximin with P-glycoprotein inhibitors such as cyclosporine. In patients with hepatic insufficiency; The potential additive effect of decreased metabolism and concomitant use of P-glycoprotein inhibitors may further increase systemic exposure to rifaximin.

Color change in urine:

As with all other rifamycin derivatives, the systemic absorption of rifaximin is negligible (less than 1%). Although the absorption of the drug is at very low levels, patients should be informed that a reddish discoloration of the urine may occur due to the drug.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions have been identified to date.

There is no experience of administering rifaximin to persons using another rifamycin antibacterial agent to treat a systemic bacterial infection.

In vitro data indicate that rifaximin does not inhibit major cytochrome P-450 (CYP) drug metabolism enzymes (CYPslA2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4). In in vitro induction studies, rifaximin did not induce CYP1A2 and CYP2B6 but weakly induced CYP3A4.

In clinical drug interaction studies in healthy subjects, it was observed that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates. However, the use of rifaximin in patients with hepatic insufficiency shows higher systemic exposure compared to healthy volunteers. Therefore, exposure of CYP3A4 substrates (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives) concomitantly used with rifaximin may be reduced in patients with hepatic impairment.

Increases and decreases in international normalized ratios have been reported in patients who were protected from warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully

followed by adding or cutting rifaximin. Oral anticoagulants may require dose adjustments.

An in vitro study suggested that rifaximin is a moderate substrate of p_glycoprotein (p-gp) and is metabolized by CYP3A4. It is not known whether concomitant use of rifaximin with drugs that inhibit the CYP3A4 enzyme increases the systemic exposure to rifaximin.

In healthy subjects, concomitant administration of a single dose of rifaximin (550 mg) and cyclosporine (600 mg), a potent p-glycoprotein inhibitor, resulted in a mean 83-fold and 124-fold increase in rifaximin Cmax and AUC. The clinical significance of the increase in systemic exposure is unknown.

Potential drug-drug interactions at levels of transport systems were investigated in *in vitro* studies, and these studies suggest that clinical interactions are not expected between rifaximin and other compounds that are excreted by p-gp and other transport proteins.

4.6 Pregnancy and lactation

General advice

The pregnancy category is C.

Women of childbearing potential/Contraception

No data are available to support specific recommendations in women of childbearing potential. Women of childbearing potential should use contraceptives that are considered medically effective during treatment.

Pregnancy period

There are no or very limited clinical data on the use of rifaximin in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/ embryonal/ fetal development/ parturition or postnatal development (see section 5.3).

Rifaximin was not teratogenic in rats and rabbits.

There are no adequate and well-controlled studies in pregnant women.

As a precaution, the use of rifaximin is not recommended during pregnancy.

The risk/benefit ratio of COLIDUR FORT should be evaluated in detail by the doctor and its use should be decided accordingly.

Lactation period

It is not known whether rifaximin or its metabolites are excreted in breast milk. Therefore, a potential risk to breastfed children cannot be excluded. The harm of breastfeeding for the child and the benefit of COLIDUR FORT therapy for the nursing mother should be taken into account when deciding whether to discontinue breast-feeding or treatment with COLIDUR FORT.

Reproductive ability / Fertility

There are no studies on the effect of rifaximin on reproductive ability in humans.
Animal studies do not indicate direct or indirect harmful effects on male or female fertility. (See Section 5.3 Preclinical safety data).

4.7 Effects on the ability to drive and use machines

It has been reported to cause dizziness in clinical studies, but this effect is negligible. Therefore, it is recommended to be careful when driving and using machines.

4.8 Undesirable effects

Adverse events are ranked by system organ class and frequency using the following approach: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Clinical studies:

Rifaximin has been compared to placebo and other antibiotics in double-blind clinical studies and clinical pharmacology studies, and quantitative safety data are available.
Note: A significant number of the undesirable effects listed (especially gastrointestinal ones) may also result from the disease being treated. It has been reported with the same frequency as those reported with placebo in clinical trials.
Adverse reactions thought to be related to rifaximin from clinical trials taking rifaximin for the treatment of diarrhea are categorized by organ system and frequency.
The safety of rifaximin in patients with remitting hepatic encephalopathy has been evaluated in two studies. One of these studies; one randomized, double-blind, placebo-controlled phase 3 study, the RFHE300l study, and the RFHE3002, a long-term, open-label study.

In the RFHE300l study, when comparing 140 patients using rifaximin 550 mg twice daily for 6 months and 159 patients receiving placebo; In study RFHE3002, of 322 patients (152 patients from study RFHE3001), 66% were treated with rifaximin 550 mg twice daily for 12 months and 39% for 24 months (mean exposure 512.5 days).
In addition, a total of 152 hepatic encephalopathy patients in three supportive studies were treated for 14 days.
He received rifaximin at doses ranging from 600 to 2400 mg daily for up to
The table below shows all adverse reactions from the placebo-controlled study RFHE3001, the long-term study RFHE3002, and post-marketing adverse reactions that occurred at an incidence > 5% in patients treated with rifaximin and at a higher incidence (≥1%) in patients receiving placebo:

Infections and infestations:
Uncommon: Clostridium infection, urinary tract infection, candidiasis
Rare: pneumonia, cellulitis, upper respiratory tract infection, rhinitis

Diseases of the blood and lymphatic system:
Uncommon: Anemia
Not known: Thrombocytopenia

Immune system disorders:
Not known: Anaphylactic reactions, angioedema, hypersensitivity

Metabolism and nutrition diseases:
Uncommon: Anorexia, hyperkalaemia
Rare: dehydration

Psychiatric diseases:
Common: Depression
Uncommon: Confusional state, anxiety, insomnia, hypersomnia

Nervous system diseases:
Common: Dizziness, headache

Uncommon: Balance disorder, amnesia, convulsions, attention deficit, hypoaesthesia, memory impairment

Vascular diseases:

Uncommon: Sudden hot flashes.

Rare: Hypertension, hypotension

Not known: Presyncope, syncope

Respiratory, thoracic and mediastinal diseases:

Common: dyspnoea

Uncommon: Pleural effusion

Rare: chronic obstructive pulmonary disease

Gastrointestinal diseases:

Common: Upper abdominal pain, abdominal bloating, diarrhoea, nausea, vomiting, ascites.

Uncommon: Abdominal pain, esophageal variceal bleeding, dry mouth, stomach discomfort

Rare: constipation

Hepatobiliary diseases:

Not known: Abnormal liver function tests

Skin and subcutaneous tissue diseases:

Common: pruritus, rash

Not known: Dermatitis, eczema

Musculoskeletal, connective tissue and bone diseases:

Common: muscle spasm, arthralgia

Uncommon: myalgia

Rare: back pain

Kidney and urinary tract diseases:

Uncommon: dysuria, pollakiuria

Rare: proteinuria

General disorders and administration site conditions

Common: peripheral edema

Uncommon: edema, fever

Rare: asthenia

Injury and poisoning

Uncommon: Fall

Rare: confusion, procedural pain

Researches:

Not known: International normalized ratio anomalies.

4.9 Overdose and its treatment

In clinical studies in patients with traveler's diarrhea, doses up to 1,800 mg/day have been tolerated by patients without clinical signs. In fact, patients/subjects with normal intestinal flora were given rifaximin at a dose of 2400 mg daily for 7 days and no clinical symptoms related to the high dose were observed.

In the treatment of rifaximin overdose, symptomatic treatments and appropriate supportive treatments are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory – anti-infective drugs.

ATC code: A07AA11

Mechanism of action

Rifaximin is an antibacterial agent of the rifamycin class, which irreversibly binds to the beta subunit of the bacterial enzyme DNA-bound RNA polymerase, thereby inhibiting bacterial RNA synthesis.

Rifaximin has a broad antimicrobial spectrum against most Gram positive and negative, aerobic and anaerobic bacteria responsible for intestinal infections.
Due to the very low absorption from the gastrointestinal tract, rifaximin acts locally in the intestinal lumen and is not clinically effective against invasive pathogens.

resistance mechanism

The basic mechanism of acquisition of rifaximin resistance involves a mutation in the rpoB gene encoding bacterial RNA polymerase.
The incidence of resistant subpopulations among bacteria isolated from wandering diarrhea patients is very low.
Clinical studies investigating changes in the susceptibility of intestinal flora in persons affected by wandering diarrhea have failed to detect the emergence of drug-resistant Gram-positive (e.g. Enterococci) and Gram-negative (E. coli) organisms over a three-day period on treatment with rifaximin.
Resistance development in normal intestinal bacterial flora; was investigated repeatedly with high doses of rifaximin in healthy volunteers and Inflammatory Bowel Disease patients. Rifaximin-resistant strains evolved, but were unstable and did not colonize the gastrointestinal tract or replace rifaximin-susceptible strains. Resistant strains disappeared rapidly when treatment was discontinued.
Experimental and clinical data suggest that treatment of patients with migratory diarrhea and Rifaximin harboring *Mycobacterium tuberculosis* or *Neisseria meningitidis* strains should not be selected for rifampicin resistance.

Sensitivity

Rifaximin is an unabsorbed antibacterial agent. In vitro susceptibility tests cannot be used to confidently establish the susceptibility or resistance of bacteria to rifaximin. Insufficient data are available to support a clinical breakpoint setting for sensitivity testing.
Rifaximin was evaluated in vitro on pathogens that cause diarrhea in travelers. These pathogens are: ETEC (Enterotoxigenic E. coli), EAEC (Enteroaggregative E. coli), Non-V cholerae vibrios. For the bacterial isolates tested, the MIC90 was 32 µg/ml, which is readily available in the intestinal lumen due to high fecal rifaximin concentrations.

Clinical efficacy

The efficacy and safety of rifaximin 550 mg twice daily given in adult patients with hepatic encephalopathy in remission were established in a Phase 3 study, the 6-month, randomized, double-blind, placebo-controlled study RFHE300l. In this study, 299 patients were randomized to treatment with rifaximin 550 mg (n=140) or placebo (n=159) for 6 months. More than 90% of patients in both groups were co-treated with lactulose. Patients with a MELD score >25 were excluded from the study.

The primary endpoint was defined as the time of hepatic encephalopathy attack and these patients were excluded from the study. During the 6-month study period, episodes of hepatic encephalopathy occurred in 31 of 140 (22%) patients in the rifaximin group and 73 (46%) of 159 patients in the placebo group. Compared with placebo, rifaximin reduced the risk of hepatic encephalopathy attacks by 58% ($p < 0.000l$) and the risk of hepatic encephalopathy-related hospitalization by 50% ($p < 0.013$).

The long-term efficacy and safety of rifaximin therapy was evaluated in the RFHE3002 study in 322 patients who went into remission. In this study, patients received rifaximin 550 mg twice daily for at least 24 months. Of the patients enrolled in the study, 152 (70 in the rifaximin group and 82 in the placebo group) were recruited from the RFHE300l study, and 170 patients were recruited as new patients. Rifaximin or placebo was used in combination with lactulose in 88% of patients.

Treatment with rifaximin for 24 months (OLE study RFHE3002) did not result in any loss in patients' protection against an attack of hepatic encephalopathy or in reducing the hospital burden.

5.2 Pharmacokinetic properties

General features

Absorbation:

Pharmacokinetic studies in rats, dogs, and humans showed virtually no absorption (less than 1%) of rifaximin after oral administration. Plasma levels (minimum 10 ng/ml) may be negligible following administration of rifaximin at therapeutic doses in healthy volunteers and patients with intestinal mucosa (Inflammatory Bowel Disease). Systemic absorption of rifaximin is increased but not clinically increased within 30 minutes of a fatty breakfast in extensive applications.

Distribution:

Rifaximin is moderately bound to human plasma proteins. In vivo, when rifaximin is administered in healthy subjects, the mean protein binding rate is 67.5%, compared to 62% in patients with hepatic impairment.

Biotransformation:

Analysis of the fecal extracts showed that rifaximin was present as the intact molecule; this means that it is not degraded or metabolized during its passage through the gastrointestinal tract.

In a study using radioactive rifaximin, the urinary dose of rifaximin excretion was 0.025%, and <0.01% of the dose found was desacetylrifaximin, the only metabolite of rifaximin detected in humans.

Elimination:

A study with radioactive rifaximin shows that 14C-Rifaximin is immediately and completely excreted in the faeces (96.9% of the administered dose). The urinary recovery of 14C rifaximin does not exceed 0.4% of the administered dose.

Linearity / Non-Linear:

The rate and extent of systemic exposure to rifaximin in humans appears to be characterized by nonlinear (dose-dependent) kinetics, consistent with the possibility of limited absorption to the dissolution rate of rifaximin. This kinetics is consistent with the dissolution rate-limited absorption probability of rifaximin.

Special Populations:

Kidney failure

No clinical data are available on the use of rifaximin in patients with impaired renal function.

Liver failure

Clinical data available for patients with hepatic impairment were higher than systemic exposure seen in healthy subjects. Systemic exposure of rifaximin is approximately 10, 13, and 20-fold higher in patients with mild (Child-Pugh A), moderate (Child-

Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to healthy volunteers.

The increase in systemic exposure to rifaximin in patients with hepatic impairment should be interpreted in light of the gastrointestinal local action and low systemic bioavailability of rifaximin, as well as in the light of available rifaximin safety data in patients with cirrhosis.

Therefore, dose adjustment is not recommended because rifaximin acts locally.

Pediatric population

The pharmacodynamics of rifaximin has not been studied in pediatric patients of any age.

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.

A slight and transient delay in ossification was observed at 300 mg/kg/day in a rat embryofoetal development study that did not affect the normal development of the offspring. An increased incidence of fetal skeletal changes was observed in the rabbit at clinically relevant doses following oral administration of Rifaximin during pregnancy.

The clinical significance of these findings is unknown.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Core tablet:

Sodium starch glycolate

Microcrystalline cellulose 200

Colloidal silicon dioxide

Magnesium stearate

Glycerol distearate

Talc

Film coating:

* Opadry OY-S 34907 Pink

*Composition: hypromellose, titanium dioxide, propylene glycol, red iron oxide, disodium EDTA

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C and in its original packaging.

Keep out of sight and reach of children and in its package.

6.5 The nature and content of the packaging

PVC / PVDC - Aluminum blister 42 film tablets / 1 box, with instructions for use

6.6 Disposal of residues from the medicinal product for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. LICENSE HOLDER

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8. LICENSE NUMBER

2021/117

9. FIRST LICENSE DATE/ LICENSE RENEWAL DATE

First license date: 21.04.2021

License renewal date:

10. RENEWAL DATE OF SPC

29.04.2021