Summary of Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

Colidur 200 mg Film Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifaximin	200 mg

See 6.1 for all excipients.

3 PHARMACEUTICAL FORM

Film tablet

Pink circular film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Acute gastrointestinal infection, travelers' diarrhea,
- Treatment of hyperamonemi as co-adjuvant.
- Treatment of diarrhea dominant irritable bowel syndrome

4.2 Posology and method of administration

Posology / Term and frequency of administration:

Amount and frequence of doses can be changed according to doctor suggestion.

The duration of treatment should not exceed 3 days unless otherwise advised by the doctor. The duration of treatment should be determined by the physician according to the clinical response of the patient.

Situation of repeated treatment, treatment should be splited up to non-drug period for 20-40 days.

Total time of periodic treatment should be determined to clinical response of patients.

Recommended dose:

Acute gastrointestinal infection, travelers' diarrhea:

Adults: 1 tablet for every 8 hours (600mg rifaximin)

Treatment of hyperamonemi as co-adjuvant:

Aduls: 2 tablet for 8 hours (1200mg rifaximin)

Treatment of diarrhea dominant irritable bowel syndrome:

Adults: 2 tablets for 8 hours (1200 mg rifaximin)

Method of administration:

It is taken orally with a glass of water. COLIDUR could be taken with or without food.

Special populations:

Patients with renal/hepatic impairment: Clinical data is not presented for patients with renal impairment.

Dose adjustment should not be recommended for patients with hepatic impairment, because of limited systemic absorption of rifaximin.

Pediatric population: Efficacy and safety of the medicine is not proved in children under 18 years.

Geriatric population: Experience with geriatric patients is limited. But the studies showed that tolerability is high.

4.3 Contraindications

- Colidur 200 mg Film Tablets are contraindicated in patients with a hypersensitivity to rifaximin, to any rifamycin (e.g rifampicin or rifabutin) any of the components in Colidur 200 mg Film Tablets (listed in section 6.1).
- If you have a fever
- If you passed 8 or more unformed stools in the last 24 hours
- If you have constipation, abdominal pain and vomiting caused by blockage of the bowel
- It must not be used in patients with intestinal obstruction or lesions of severe intestinal ulceration even if partial.

4.4 Special warnings and special precautions for use

Clinical data have shown that rifaximin is not effective in the treatment of travellers' diarrhoea caused by invasive enteric pathogens such as *Campylobacter jejuni*, *Salmonella* spp. *and Shighella*, which typically produce dysentery-like diarrhoea characterised by fever, blood in the stool and high stool frequency.

If symptoms worsen treatment with rifaximin should be interrupted.

If symptoms have not resolved after 3 days of treatment, or recur shortly afterwards, a second course of rifaximin should not be administered.
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.
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.
Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor such as ciclosporin is needed (see section 4.5).
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 (see section 4.5).

Pediatric population
COLIDUR 200 mg Film Tablet is not recommended for children (under 18 years old).

4.5 Interaction with other medicinal products and other forms of interaction
No interaction is identified.

There is no experience with the administration of rifaximin to a person using another rifamycin antibacterial agent to treat a systemic bacterial infection.

In vitro data indicate that rifaximin does not inhibit major cytokine P-450 (CYP) drug metabolizing enzymes (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4).

In vitro, rifaximin does not induce CYP1A2 and CYP2B6, but P450 indicates that the cytochrome is a weak inducer of CYP3A4 isoenzyme.

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 CYP3A4 can increase the systemic exposure of rifaximin.

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

The clinical significance of this increase in systemic exposure is unknown.

The potential for drug-drug interactions to occur at the level of gut 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).

No drug interaction studies investigating the concomitant intake of rifaximin and other drugs that might be used during an episode of travellers' diarrhoea (e.g. loperamide, charcoal) are available.

In case of administration of charcoal, rifaximin should be taken at least 2 hours after that administration.

Additional information for special populations:

No interaction study is conducted for special populations

Pediatric population:

No interaction study is conducted for pediatric population

4.6 Pregnancy and lactation

General Advice

Pregnancy category C

Women of Childbearing Potential /Contraception

In women of childbearing potential there is no data supporting special advice. Women of childbearing potential should use contraceptive methods which are medically accepted to be safe.

Pregnancy

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

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

Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3). The clinical relevance of these findings in humans is unknown.). The clinical significance of these findings in humans is unknown.

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 in direct harmful effects with respect to male and female fertility. (see also section 5.3 Preclinical safety data)

4.7 Effects on ability to drive and use machines

In clinical controlled trials dizziness and somnolence have been reported but rifaximin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical trials on subjects taking rifaximin for tourist diarrhea treatment have categorized possible adverse reactions related to rifaximin, organ system and frequency.

Post-marketing experience

Undesirable effects have been reported during the use of rifaximine after approval. The frequency of these reactions is not known (unpredictable from available data).

The following adverse events are presented according to system/organ classification.

The classification of frequency: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

Infections and Infestations:

Uncommon: candidiasis, herpes simplex, nasopharyngitis, pharyngitis, upper respiratory tract infection.

Frequency not known: Clostridial infections.

Blood and Lymphatic System Disorders:

Uncommon: Lymphocytosis, monocytosis, neutropenia

Frequency not known: Thrombocytopenia.

Immune system disorders:

Frequency not known: Anaphylactic reactions and hypersensitivity.

Metabolic and Nutritional Disorders:

Uncommon: Decreased appetite, dehydration.

Psychiatric Disorders:

Uncommon: Insomnia, abnormal dreams, depressed mode, nervousness.

Nervous System Disorders:

Common: Headache, dizziness

Uncommon: Migraine, hypoesthesia, parasthesia, sinus headache, somnolence.

Frequency not known: Presyncope (state of being like fainting).

Eye disorders:

Uncommon: Diplopia

Ear and Labyrinth Disorders:

Uncommon: Vertigo, ear pain

Cardiac disorders:

Uncommon: Palpitation

Vascular Disorders:

Uncommon: Hot flush, increased blood pressure

Respiratory, Thoracic, and Mediastinal Disorders:

Uncommon: Dyspnoea, nasal congestion, cough, Oropharyngeal pain, Rhinorrhea (nasal discharge), dry throat

Gastrointestinal Disorders:

Common: Constipation, abdominal pain, abdominal distension, diarrhea, flatulance, nausea, rectal tenesmus, defecation urgency, vomiting

Uncommon: Assit, dyspepsia, gastrointestinal motility impairment, upper abdominal pain, hematochezia, Mucous stools, solid faeces, dry lips, loss of taste sensation.

Hepatiobiliary disorders:

Uncommon: Increase of aspartat aminotransferase

Frequency not known: Liver function test abnormalities.

Skin and Subcutaneous Tissue Disorders:

Uncommon: rash, eruptions, exanthema (viral rash disease), maculation and sunburn.

Frequency not known: angioedema, dermatitis, dermatitis exfoliative, eczema, erythemas, pruritus, purpura, urticaria

Musculoskeletal, Connective Tissue, and Bone Disorders:

Uncommon: Back pain, muscle spasms, myalgia, muscle weakness, neck pain

Renal and Urinary Disorders:

Uncommon: Glycosuria, pollakiuria, polyuria, blood in urine, proteinuria.

Reproductive system disorders:

Uncommon: Polymenorrhea

General Disorders and Administration Site Conditions:

Common: Pyrexia

Uncommon: Asthenic conditions, peripheral edema, Influenza like illness, chills, cold sweat, hyperhidrosis (excessive sweating), pain and discomfort.

Investigations:

Frequency not known: International normalized rate anomalies.

4.9 Overdose

In clinical trials with patients suffering from travellers' diarrhoea doses of up to 1800 mg/day have been tolerated without any severe clinical signs.

Dosages of up to 2400 mg/day for 7 days in patients/subjects with normal bacterial flora rifaximin did not result in any relevant clinical symptoms related to the high dosage.
In case of overdose symptomatic treatments and supportive care are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal, anti-infective agents- antibiotics
ATC code: A07AA11

Mode of Action

Rifaximin is an antibacterial agent of the rifamycin class that binds irreversibly to the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA and protein synthesis.

Rifaximin has a wide efficacy spectrum which involves most of gram positive, gram negative, aerob and anaerob bacteria responsible for gastrointestinal infections.

Due to the very low absorption from the gastrointestinal tract, rifaximin acts locally in the intestinal lumen and is not effective against clinically invasive pathogens.

Mechanism of resistance

The main mechanism of acquiring resistance to rifaximin appears to involve a mutation in the *rpoB* gene encoding the bacterial RNA polymerase.
The incidence of resistant subpopulations among bacterial isolates from patients who suffer from diarrhea is very low.
Clinical trials investigating alterations in intestinal flora sensitivity of people affected by tourist diarrhea could not detect the emergence of infrequently resistant Gram-positive (eg Enterococci) and Gram-negative (E. coli) organisms for a period of three days 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 tourist diarrhea and rifaximin treatment of patients with Mycobacterium tuberculosis or Neisseria meningitidis strains will not be selected 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 pathogens causing traveller's diarrhoea. These pathogens were: ETEC (Enterotoxigenic *E. coli*), EAEC (Enteroaggregative *E. coli*), Non-V *cholerae vibrios*. The MIC90, for the bacterial isolates tested, was 32 µg/ml, which can easily be achieved in the intestinal lumen due to high faecal concentrations of rifaximin.

5.2 Pharmacokinetic properties

Absorption:

Following the 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).

Systemic absorption of rifaximin is increased but not by a clinically relevant extent by administration 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 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.

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 embryofoetal 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.

In the rabbit, following oral administration of Rifaximin during gestation, an increase in the incidence of fetal skeletal variations was observed at clinically relevant doses.
The clinical relevance of these findings is unknown

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Sodium starch glycolate

Microcrystalline cellulose pH 200

Colloidal silicon dioxide

Magnesium stearate

Talc

Glyceryl palmitostearate

Coating:

Opadry OY-S 34907 Pink (Hypromelllose**,** Titanium Dioxide**,** Propylene glycol, Red iron oxide, Disodium EDTA)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Store in a dry place and at room temperature below 25°C.

Store in the original package and keep the product out of the reach and sight of children.

6.5 Nature and contents of container

12 film-coated tablets packed in PVC/PVDC/Aluminium blisters in a carton box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Drogsan İlaçları San. Tic. A.Ş.

Oğuzlar Mah. 1370. Sok. 7/3

Balgat/Ankara – TURKEY

8 MARKETING AUTHORIZATION NUMBER

222 / 65 (in Turkey)

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29.12.2009

10 DATE OF REVISION OF THE TEXT

06/09/2018