SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Xifaxanta 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains:
Rifaximin 200 mg

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Pink, circular biconvex film-coated tablets, with “AW” embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Xifaxanta 200mg film-coated tablets are indicated for the treatment of traveller’s diarrhoea that is not associated with any of:

Fever
Bloody diarrhoea
Eight or more unformed stools in the previous 24 h
Occult blood or leucocytes in the stool

Xifaxanta 200mg film-coated tablets may shorten the duration of diarrhoea when this is associated with non-invasive strains of *E. coli* (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology
200mg every 8 hours for three days (total 9 doses).

Rifaximin must not be used for more than 3 days even if symptoms continue and a second course of treatment must not be taken (see section 4.4).

Rifaximin can be administered with or without food

Paediatric population
The safety and efficacy of Xifaxanta 200mg film-coated tablets in children (aged less than 18 years) have not been established

Elderly
No dosage adjustment is necessary as the safety and efficacy data of Xifaxanta 200mg film-coated tablets showed no differences between the elderly and the younger patients.

Hepatic impairment
A dosage adjustment for patients with hepatic insufficiency is not necessary (see section 5.2).

Renal impairment
Although dosing change is not anticipated, caution should be used in patients with impaired renal function (see section 5.2).

Method of administration
Orally with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance, to any rifamycin (e.g. rifampicin or rifabutin) or to any of the excipients (listed in section 6.1).

Cases of intestinal obstruction.

4.4 Special warnings and precautions for use

Severe skin reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported [frequency unknown] in association with rifaximin treatment. Most of the cases were reported in patients with liver disease (such as cirrhosis or hepatitis). At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, rifaximin should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of rifaximin, treatment with rifaximin must not be restarted in this patient at any time.

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.

Clostridioides 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).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Paediatric population
Xifaxanta 200 mg film-coated tablets are not recommended for use in children (<18 years old).

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 vitro data show that rifaximin did not induce CYP1A2 and CYP 2B6 but is a weak inducer of the CYP3A4 isoenzyme of the P450 cytochrome.

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 thesestudies 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.

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 (see section 5.3). The clinical relevance of these findings in humans is unknown.

As a precautionary measure, use of rifaximin during pregnancy is not recommended.

Breast-feeding

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.

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

Summary of safety profile
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with rifaximin treatment. Most of the cases were reported in patients with liver disease (such as cirrhosis or hepatitis) (see section 4.4).

In clinical studies in subjects who received rifaximin for treatment of travellers' diarrhoea, Adverse Reactions considered as being at least possibly related to rifaximin have been categorised by organ system and frequency.

Post-marketing experience
During post-approval use of rifaximin further undesirable effects have been reported. The frequency of these reactions is not known (cannot be estimated from the available data).
Frequency categories are defined using the following convention:
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).

MedDRA System Organ Class	**Common**	**Uncommon**	**Frequency not Known**
Infections and infestations		Candidiasis, Herpes simplex Nasopharyngitis Pharyngitis Upper respiratory tract infection	Clostridial infections
Blood and lymphatic system disorders		Lymphocytosis Monocytosis Neutropenia	Thrombocytopenia
Immune system disorders			Anaphylactic reactions Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite Dehydration	
Psychiatric disorders		Abnormal dreams Depressed mood Insomnia Nervousness	

MedDRA System Organ Class	Common	Uncommon	Frequency not Known
Nervous system disorders	Dizziness Headache	Hypoesthesia Migraine Paraesthesia Sinus headache Somnolence	Presyncope
Eye disorders		Diplopia	
Ear and labyrinth disorders		Ear pain Vertigo	
Cardiac disorders		Palpitations	
Vascular disorders		Blood pressure increased Hot flush	
Respiratory, thoracic, and mediastinal disorders		Cough Dry throat Dyspnoea Nasal congestion Oropharyngeal pain Rhinorrhea	
Gastrointestinal disorders	Abdominal pain Constipation Defecation urgency Diarrhoea Flatulence Abdominal distension Nausea Vomiting Rectal tenesmus	Abdominal pain upper Dry lips Dyspepsia Gastrointestinal motility disorder Faeces hard Haematochezia Mucous stools Taste disorders	
Hepatobiliary disorders		Aspartate aminotransferase increased	Liver function test abnormalities
Skin and subcutaneous tissue disorders		Rashes, eruptions and exanthemas Sunburn	Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Angioedema Dermatitis Dermatitis exfoliative Eczema Erythemas Pruritus Purpura Urticarias

MedDRA System Organ Class	Common	Uncommon	Frequency not Known
Musculoskeletal and connective tissue disorders		Back pain Muscle spasms Muscular weakness Myalgia Neck pain	
Renal and urinary disorders		Blood in urine Glycosuria Pollakiuria Polyuria Proteinuria	
Reproductive system and breast disorders		Polymenorrhoea	
General disorders and administration site conditions	Pyrexia	Asthenic conditions Chills Cold sweat Hyperhidrosis Influenza like illness Oedema peripheral Pain and discomfort	
Investigations			International normalised ratio abnormalities

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Dosages of up to 2400mg/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.

The product Xifaxanta contains rifaximin (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

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 synthesis.

Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and -negative, aerobic and anaerobic bacteria responsible for intestinal infections.

Due to the very low absorption from the gastro-intestinal tract rifaximin in the polymorph α form is locally acting in the intestinal lumen and clinically not effective against 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 bacteria isolated from patients with traveller's diarrhoea was very low.

Clinical studies that investigated changes in the susceptibility of intestinal flora of subjects 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 of traveller's diarrhoea 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 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 32μg/ml, which can easily be achieved in the intestinal lumen due to high faecal concentrations of 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 virtually not absorbed (less than 1%). 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 10ng/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 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 embryofoetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300mg/kg/day. In the rabbit, following oral administration of Rifaximin during gestation, an increase in the incidence of foetal skeletal variations was observed at clinically relevant doses.

The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycolate type A
glycerol distearate
colloidal anhydrous silica
talc
microcrystalline cellulose

Tablet coat
hypromellose
titanium dioxide (E171)
disodium edetate
propylene glycol
red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Original packing: 3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC -Aluminium blister pack containing 9 tablets.

7 MARKETING AUTHORISATION HOLDER

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7 MARKETING AUTHORISATION HOLDER

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