SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OFTHE MEDICINAL PRODUCT

ALFA NORMIX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains:
Rifaximin 200 mg

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrointestinal disorders sustained by Rifaximin-sensitive bacteria such as acute gastrointestinal infections, traveler's diarrhea, intestinal overgrowth syndrome, hepatic encephalopathy, symptomatic uncomplicated diverticular disease of the colon and chronic bowel inflammation.
Prophylaxis of infective complications in colorectal surgery.

4.2 Posologyand method of administration

Adults and children over 12 years of age: from 1 film-coated tablet every 8 hours to 2 film- coated tablets every 8 - 12 hours (equal to 600 - 1200 mg of Rifaximin)
The duration of treatment should not exceed 7 days and should be determined by the clinical response of the patients.
In the cases in which repeated courses of treatment are required, each course of treatment should be separated by a wash-out period of 20 to 40 days.
The total duration of the intermittent therapy should be determined by the adequacy of the clinical response of the patients.

Doses may be modified in quantity and frequency, according to the physician's advice.

Method of administration Orally
with a glass of water.
Rifaximin can be administered with or without food.

Elderly
No dosage adjustment is necessary as the safety and efficacy data of ALFA NORMIX showed no differences between the elderly and the younger patients.

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic insufficiency (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).

Paediatric Population
The safety and efficacy of rifaximin in children younger than 12 years of age have not been established. Currently available data are described in section 5.1, but no dosage recommendation can be made.

4.3 Contraindications

Hypersensitivity to the active substance, rifamycin-derivatives or to any of the excipients listed in section 6.1.
Cases of intestinal obstruction. Rifaximin should not be administered in patients with diarrhea complicated by fever or blood in stool.

4.4 Special warnings and special precautions for use

Clinical data have shown that rifaximin is not effective in the treatment of intestinal infections due to invasive enteric pathogens such as *Campylobacter jejuni, Salmonella* spp. *and Shighella*spp., which typically cause diarrhoea, fever, blood in the stool and high stool frequency. Rifaximin should be discontinued if diarrhoea symptoms get worse or persist for more than 48 hours and an alternative antibiotic therapy should be considered.
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.
Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor such as cyclosporine is needed (see section 4.5).
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.

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 desire level of anticoagulation (see section Drug Interactions).

ALFA NORMIX 200 mg film-coated tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'**.**

4.5 Interaction with other medicaments 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 *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 increase in international normalized ratio have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ration 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 Pglycoprotein (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 cyclosporine (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∞. The clinical significance of this increase in systemic exposure is unknown.
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).
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 indirect harmful effects with respect to male and female fertility.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence have been reported in clinical controlled trials. However, rifaxamin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials
During double-blind controlled clinical trials or clinical pharmacology studies, rifaximin effects have been compared to placebo and other antibiotics, therefore quantitative safety data are available.
Note: The majority of adverse reactions listed (in particular for gastrointestinal disorders) may also be attributable to the underlying diseases being treated and have been reported during clinical trials at the same frequency as the one reported in placebo-treated patients. 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	Not known
Infections and infestations		Candidiasis, Herpes simplex, Nasopharyngitis, Pharyngitis, Upper respiratory tract infection	Clostridial infection

Blood and lymphatic system disorder		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	
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, *Ascites*, Dry lip, Dyspepsia, Gastrointestinal motility disorder, Faeces hard, Haematochezia, Mucous stools, Taste disorders	

Hepatobiliary disorders		Aspartate aminotransferase increased	Liver function tests abnormalities
Skin and subcutaneous tissue disorders		Rashes, Eruptions and exanthemas, Sunburn[1]	Angioedema, Dermatitis, Dermatitis exfoliative, Eczema, Erythemas, Pruritus, Purpura, Urticarias
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 abnormal

1 As the investigator reported "sunburn" this is not be considered as generally referring to photosensitivity but actually to "sunburn".

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 the national reporting system: Scientific Centre of Drug and Medical Technologies Expertise, website: https://www. pharm.am

4.9 Overdose

In 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 overdosage, symptomatic treatments and supportive care are suggested.

5. PHARMACOLOGICAL PROPERTIES

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

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: intestinal, anti-infective - antibiotics - Class ATC A07AA11

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 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, even though these bacteria are susceptible *in vitro*. The broad antibacterial spectrum of rifaximin also enables it to decrease the intestinal bacterial load which is responsible for or is involved in several pathological conditions. Consequently rifaximin is able to reduce:

- the bacterial production of ammonia and other toxic substances that in case of severe liver disease with impaired detoxification activity are involved in the pathogenesis and symptomatology of hepatic encephalopathy

- hyperproliferation of bacteria in the intestinal bacteria overgrowth syndrome

- the presence of bacteria in the colon diverticula, that may contribute to inflammation in and around the diverticular sac and may play a key role in developing diverticular disease symptoms and complications

- the antigenic stimuli that, in presence of genetically determined defects in mucosal immunoregulation and/or barrier function, may induce or perpetuate chronic bowel inflammation

- the risk of infective complications in colorectal surgery.

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. 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 in four different areas of the world. These pathogens were: ETEC (Enterotoxigenic *E. coli*), EAEC

(Enteroaggregative *E. coli*), *Salmonella* spp., *Shigella* spp., Non-V *cholerae vibrios*, *Plesiomonas* spp., *Aeromonas* spp., *Campylobacter* spp. 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. 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 studies in patients with traveller's diarrhoea demonstrated clinical effectiveness of rifaximin against ETEC (Enterotoxigenic *E. coli*) and EAEC (Enteroaggregative *E. coli*). These bacteria are predominantly responsible for causing traveller'sdiarrhoea in subjects travelling to Mediterranean countries or tropical and subtropical regions.

Paediatric population

The efficacy, posology and safety of rifaximin in paediatric patients younger than 12 years of age have not been established.

Literature review identified 9 efficacy studies in the paediatric population which have included 371 children, 233 having received rifaximin. Most of enrolled children aged more than 2 years. The characteristic which was present in all studies was diarrhoea of bacterial origin (proven before, during or after treatment)

The data (the studies per se and a meta-analysis) show that there is a positive trend to demonstrate efficacy of rifaximin in a special condition [acute diarrhoeas (mainly recurrent or relapsing) which are known or supposed to be caused by non-invasive rifaximin sensitive bacteria such as *Escherichia coli*].

The mostly used dosage in children from 2 - 12 years in these limited studies with few patients was in the range of 20-30 mg/kg/d in 2 to 4 administrations (see section 4.2).

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%). 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). A clinically not relevant 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 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. Despite of this, 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 300 mg/kg/day. In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed.

The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

One film-coated tablet contains:

glycolate sodium starch, glycerol distearate, colloidal anhydrous silica, talc, microcrystalline cellulose, hypromellose titanium dioxide E171, disodium edetate, propylene glycol, red iron oxide E172.

6.2 Incompatibilities

None known.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

200 mg film-coated tablets

One blister pack constituted by PVC-PE-PVDC/Aluminium containing 12 film-coated tablets

6.6. Instructions for use

Please refer to the paragraph 4.2.

7. MARKETING AUTHORIZATION HOLDER

Alfasigma S.p.A.

Via Ragazzi del ’99, 5 - 40133 Bologna (BO) - Italy

8. MARKETING AUTHORIZATION NUMBER
7686

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
1st February 2008

12. DATE OF REVISION OF THE TEXT