SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NORMIX 200-mg film-coated tablets
NORMIX 2 g/100-ml granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets
Each film-coated tablet contains 200 mg rifaximin.

Granules for oral suspension
100 ml of reconstituted suspension contains 2 g rifaximin.

Excipients with known effects: the granules for oral suspension contain sucrose and sodium benzoate.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Granules for oral suspension.

4. CLINICAL INFORMATION

4.1 Therapeutic indications

- Acute and chronic intestinal infections sustained by Gram-positive and Gram-negative bacteria; diarrhoeic syndrome.
- Diarrhoea caused by an altered equilibrium in the intestinal microbial flora (summer diarrhoea, traveller's diarrhoea, enterocolitis).
- Pre- and postoperative prophylaxis of infective complications in gastrointestinal tract surgery.
- Coadjuvant in treatment of hyperammonemia

4.2 Posology and method of administration

Anti-diarrhoeic treatment
Recommended dose*:*
- Adults and children over 12 years: one 200 mg tablet or 10 ml of oral suspension (equal to 200 mg rifaximin) every 6 hours.

Pre- and postoperative treatment
Recommended dose:
- Adults and children over 12 years: two 200 mg tablets or 20 ml of oral suspension (equal to 400 mg rifaximin) every 12 hours.

Coadjuvant in treatment of hyperammonemia
Recommended dose:
- Adults and children over 12 years: two 200 mg tablets or 20 ml of oral suspension (equal to 400 mg rifaximin) every 8 hours.

This medicine can be administered with or without food.

Depending on the physician's advice these doses may be modified in quantity and frequency. Unless otherwise prescribed, treatment should not exceed 7 days.

Elderly
The pharmacokinetic of rifaximin has not been studied in elderly patients, anyway no dosage adjustment is necessary as the safety and efficacy data of NORMIX showed no differences between the elderly and the younger patients.

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic insufficiency, caution should be used in patients with severe hepatic impairment. (see section 5.2).

Renal impairment
Although no dosage change is anticipated, caution should be used in patients with impaired renal function (see section 5.2).

Pediatric 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 recommendation on a posology can be made.

Method of administration
- Film-coated tablets: orally with a glass of water.
- Granules for oral suspension: 5 ml of suspension contains 100 mg of active substance. For instructions on reconstitution of the suspension before administration see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, rifamycins or any of the excipients listed in section 6.1.
Cases of intestinal obstruction, even partial, or severe ulcerous lesions of the intestine.
Rifaximin should not be administered in patients with diarrhoea complicated by fever or blood in the stool.

4.4 Special warnings and precautions for use

Clinical data have shown that rifaximin is not effective in the treatment of intestinal infections due to invasive intestinal pathogens such as *Campylobacter jejuni* species, *Salmonella* species and *Shigella* species which typically cause diarrhoea, fever, blood in the stools and high stool frequency.
Treatment should be discontinued if the 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 the use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD or pseudomembranous colitis 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 discoloration of the urine.

Both decreases and increases in international normalized ratio -INR (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).

Normix 2 g/100 ml granules for oral suspension contains **sucrose**. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
The medicine contains 2,88 g per 10 ml of reconstituted suspension. This should be taken into account in patients with diabetes mellitus.
Normix 2g/100 ml granules for oral suspension contains 6 mg of sodium benzoate in one dose of 10 ml reconstituted suspension corresponding to 60 mg/100 ml.
It contains less than 1mmol (23mg) of sodium per 10 ml of reconstituted suspension, that is to say essentially 'sodium-free'.

Normix 200 mg film-coated tablets contains 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) which are responsible for drug metabolism (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4). In *in vitro* induction studies, rifaximin did not induce CYP1A2 and CYP2B6, but was a weak inducer of CYP3A4.

In healthy subjects, clinical drug-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 (INR) 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 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 interaction with other drugs at carrier level has been evaluated *in vitro*. These studies suggest that a clinical interaction between rifaximin and other compounds which undergo efflux via P-gp and other transport proteins (MRP2, MRP4, BCRP and BSEP) is unlikely.

Patients should take Rifaximin at least 2 hours after the administration of charcoal.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy
There are no or limited data on 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 is not known.
As a precautionary measure, use of rifaximin during pregnancy is not recommended.

Breast-feeding
It is unknown whether rifaximin and 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 on 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 rifaximin has negligible influence on the ability to drive or 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 or other antibiotics,. therefore quantitative safety data are available.

Note: Many of the adverse reactions listed (in particular gastrointestinal reactions) may be the same symptoms attributable to the underlying diseases being treated and, during clinical trials, have been reported in the same frequency in placebo-treated patients.

Post-marketing experience
During post-approval use of the product 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 convention below:

Very common (≥ 1/10); Common (≥ 1/100 < 1/10); Uncommon (≥ 1/1000 < 1/100); Rare (≥ 1/10000 < 1/1000); Very rare (< 1/10000); Not known (frequency cannot be estimated from the available data).

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Candidiasis, herpes simplex, nasopharyngitis,		Clostridial infection

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
		pharyngitis, upper-respiratory-tract infections		
Blood- and lymphatic-system disorder		Lymphocytosis, monocytosis, neutropenia		Thrombocytopenia
Immune-system disorders				Anaphylactic responses, hypersensitivity
Metabolism and nutrition disorders		Decreased appetite, dehydration		
Psychiatric disorders		Insomnia, abnormal dreams, depressed mood, nervousness		
Nervous-system disorders	Dizziness, headache	Migraine, hypoesthesia, paraesthesia, sinus headache, somnolence		Presyncope
Eye disorders		Diplopia		
Ear and labyrinth disorders		Vertigo, ear pain		
Cardiac disorders		Palpitations		
Vascular disorders		Blood pressure increased, hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, nasal congestion, dry throat, oropharyngeal pain, cough, rhinorrhea		
Gastrointestinal disorders	Constipation, abdominal pain, abdominal distension, diarrhoea, flatulence, nausea, rectal tenesmus , defecation urgency, vomiting symptoms	Ascites, dyspepsia, gastrointestinal-motility disorder, abdominal pain upper, haematochezia, mucous stools, faeces hard, dry lip, taste disorders		
Hepatobiliary disorders		Aspartate aminotransferase increased		Liver-function-test abnormalities
Skin and subcutaneous-tissue disorders		Rashes, eruptions and exanthemas, sunburn[1]		Angioedema, dermatitis, dermatitis exfoliative, eczema, erythemas, purpura, pruritus, urticarias
Musculoskeletal and connective-		Back pain, muscular weakness, muscle		

[1] As the investigator reported "*sunburn*", this is considered as actually a "*sunburn*", not as referring to photosensitivity reactions.

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
tissue disorders		spasm, neck pain, myalgia,		
Renal and urinary disorders		Blood in urine, glycosuria, pollakiuria, polyuria, proteinuria		
Reproductive-system disorders		Polymenorrhoea		
General disorders and administration-site conditions	Pyrexia	Asthenic conditions, chills, cold sweat, pain and discomfort, oedema peripheral, influenza-like illness, hyperhidrosis,		
Investigations				International normalised ratio abnormal

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions appearing after approval of the medicinal product is important as it permits continuous monitoring of the benefit/risk ratio of the product. Health operators are requested to report any suspected adverse reaction to the Italian Drug Agency, web site: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 **Overdosage**

In clinical trials with patients suffering from traveller's diarrhoea, doses of up to 1,800 mg/day have been tolerated without any severe clinical symptom. Even in patients/subjects with normal bacterial flora rifaximin at doses of up to 2,400 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. In case of recent administration the gastric emptying could be useful.

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiarrhoeals, anti-inflammatories and intestinal anti-infectives, antibiotics
Class ATC A07AA11

Mechanism of action
Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta subunit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial-RNA synthesis.

Rifaximin has a broad antibacterial spectrum against most of the Gram-positive and -negative aerobic and anaerobic bacteria.
Due to the very low absorption from the gastro-intestinal tract rifaximin in the polymorph form α is locally acting in the intestinal lumen and is clinically not effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.

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 in 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 patients with inflammatory bowel disease. 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 treatment with rifaximin of patients harbouring *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.

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
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's diarrhoea in subjects travelling to Mediterranean countries or tropical and subtropical regions.

Paediatric population

The efficacy, safety and posology of rifaximin in paediatric patients younger than 12 years of age have not been established.
A review of scientific literature identified 9 efficacy studies in the paediatric population which have included 371 children, 233 having received rifaximin. Most of the 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 most used dosage in children from 2 to 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 rat, dog and humans demonstrated that rifaximin in the polymorphic form α is practically not absorbed (less than 1%) when administered by the oral route. In pharmacokinetic comparative studies, it has been demonstrated that rifaximin in the polymorphic forms different from the α form has absorbance considerably higher.

After repeated therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (inflammatory bowel disease) the rifaximin plasma levels were negligible (less than 10 ng/ml). A clinically non-relevant increase of the rifaximin systemic absorption was observed when it was administered within 30 minutes of a high-fat meal.

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

An 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.

A study using radio-labelled rifaximin showed a urinary recovery of rifaximin of 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) kinetics, 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 increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in the light of rifaximin gastrointestinal local action and its low systemic bioavailability as well as on the basis of 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 hazards 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

Film-coated tablets
Tablet core
Sodium starch glycolate, type A
Glycerol distearate
Colloidal anhydrous silica
Talc
Microcrystalline cellulose

Tablet coating
Hypromellose
Titanium dioxide E171
Disodium edetate
Propylene glycol
Red iron oxide E172

Granules for oral suspension
Microcrystalline cellulose
Croscarmellose sodium
Pectin
Kaolin
Sodium saccharin
Sodium benzoate
Sucrose
Cherry flavouring

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Film-coated tablets and granules for oral suspension: 3 years.
The oral suspension prepared by adding water to the granules for oral suspension is stable for 7 days at room temperature.

6.4 Special precautions for storage

Film-coated tablets: this medicinal product does not require any special storage conditions.
Granules for oral suspension: for storage conditions for the reconstituted suspension see section

6.3.

6.5 **Nature and contents of container**

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

Granules for oral suspension:
Dark glass bottle, hermetically sealed with an aluminium cap, containing granules for oral suspension. A measuring spoon is enclosed with the bottle.

6.6. **Special precautions for disposal and other handling**

Granules for oral suspension
Reconstitution of suspension
Add water to the granules contained in the bottle up to the mark and shake well.
Add water again until the suspension level reaches the sign indicated.
Shake well before use.
The suspension so prepared is stable for 7 days at room temperature.

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

7. MARKETING AUTHORIZATION HOLDER

Alfasigma S.p.A.
Via Ragazzi del '99, n. 5 – 40133 Bologna (BO) - Italy

8. MARKETING AUTHORIZATION NUMBERS

NORMIX 200-mg film-coated tablets – 12 tablets:	Code No. 025300029
NORMIX 2-g/100-ml granules for oral suspension – 60-ml bottle:	Code No. 025300043

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization: 14 September 1985
Date of latest renewal: 1 June 2010

10. DATE OF REVISION OF TEXT

05 June 2021