Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Lormyx 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains: Rifaximin (polymorphic form α) 200 mg

For the full list of excipients, see section 6.1.

3. FHARMACEUTICAL FORM

Film-coated tablet
Visual nature: pink, bi-convex film-coated tablet with a diameter of 10 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

- Causal treatment of illnesses in adults and youths from the age of 12 years up caused by bacteria in the gastro-intestinal tract, sensitive to Rifaximin:
  - Non-complicated diverticular diseases
  - Hepatic encephalopathy
  - Travellers' Diarrhoea caused by non-invasive enteropathogenic bacteria

4.2 Posology and method of administration

Posology

Adults and young people from the age of 12:

- *Travellers' Diarrhoea*: 2 - 3 times a day 1 - 2 Film-coated tablets Lormyx (corresponding to 400 – 1200 mg Rifaximin (polymorphic form α))
- Non-complicated diverticular diseases, *Hepatic encephalopathy:* 2 - 3 times per day 2 film-coated tablets Lormyx (corresponding to 800 - 1200 mg Rifaximin (polymorphic form α)) per treatment cycle.

Children

The safety and effectiveness of Rifaximin (polymorphic form α) for children under the age of 12 has not been examined.
Currently available data is described in Section 5.1. However, no recommendation can be made regarding the dosage.

Method of administration

The film-coated tablets have to be taken with sufficient liquid and must not be chewed.
Taking the tablets does not depend on meals.

Duration of treatment

Travellers' Diarrhoea:

If not otherwise specified by the doctor, the duration of the treatment for Travellers' Diarrhoea must not exceed 3 days.
Non-complicated diverticular diseases, *Hepatic encephalopathy:*
The duration of a treatment cycle should not exceed 7 - 10 days. For acute treatment, a single treatment cycle is sufficient. As maintenance treatment, one cycle per month is carried out.

Patients with liver and/or kidney malfunction
Adjusting the dosage for patients with liver or kidney malfunction is not necessary.

4.3 Contraindication

- Hypersensitivity to the active substance Rifaximin (polymorphic form α) or other Rifamycin derivatives or to any of the excipients listed in section 6.1
- Intestinal obstruction

4.4 Special warnings and special precautions for use

Severe skin reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal eecrolysis (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.

During long time of treatment with high doses or in case of an existing injury of the intestinal mucosa, an absorption of smaller quantities of Rifaximin (less than 0.4 %) and a reddish colouration of the urine can occur. This is due to the colour of the active ingredient, which is red orange like that of most of the other Rifamycin antibiotics.

Due to the low absorption rate (see section 5.2), **Lormyx 200 mg** is not suitable for the treatment of systemic infections and invasive intestinal mucosal infections. The use of Rifaximin (polymorphic form α) in patients with complicated diarrhoea and fever or bloody stools is not recommended. Stop treatment with **Lormyx 200 mg** if diarrhoea symptoms persist after 24 - 48 hours and consider a change of therapy.

Clinical data have shown that Rifaximin (polymorphic form α) is not effective in the treatment of intestinal infections due to invasive enteric pathogens such as *Campylobacter jejuni, Salmonella spp. and Shigella spp.*

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial medicines, 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).

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'.

4.5 Interactions with other medicinal products and other forms of interaction

Since the absorption of orally administered Rifaximin (polymorphic form α) by the gastro-intestinal tract is negligible (less than 0.4 %), problems related to pharmacological interaction at systemic level are low.

In vitro data show that rifaximin (polymorphic form α) 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 (polymorphic form α) did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4. In healthy subjects, clinical drug interaction studies demonstrated that rifaximin (polymorphic form α) did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that rifaximin (polymorphic form α) 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 (polymorphic form α). If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of rifaximin (polymorphic form α). 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 (polymorphic form α).
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 (polymorphic form α) 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 (polymorphic form α) and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

In the case of administration of charcoal, patients should take rifaximin at least 2 hours after that administration.

4.6 Fertility, pregnancy, and lactation

Pregnancy

To date, there is no or limited data from the use of rifaximin (polymorphic form α) in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3).

The use of **Lormyx 200 mg** during pregnancy is not recommended.

Breastfeeding

It is unknown whether **Lormyx 200 mg** / metabolites are excreted in human milk. A risk to the newborn/ child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from **Lormyx 200 mg** 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

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).

Clinical Trials

During double-blind controlled clinical trials or clinical pharmacology studies, **LORMYX 200 mg** 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 **LORMYX 200 mg** further undesirable effects have been reported, whose frequency is not known.

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).

	Frequency of undesirable effects		
MedDRA System Organ Class	**Common**	**Uncommon**	**Unknown**
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 reaction, 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 (partially as signs of hypersensitivity reactions)		Rashes, Eruptions and exanthemas, Sunburn[1]	Stevens-Johnson syndrome (SJS) Toxic Epidermal Necrolysis (TEN) 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 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

Lormyx 200 mg contains rifaximin (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

5.1 Pharmaco-dynamic Properties

Pharmaco-therapeutic group: Intestinal anti-infective, antibiotics [Rifaximin (polymorphic form α)]; ATC-Code: A07AA11

Mechanism of action

Rifaximin (polymorphic form α) 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 (polymorphic form α) 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 (polymorphic form α) in its polymorph form is locally acting in the intestinal lumen and clinically not effective against invasive pathogens, even though these bacteria are susceptible in vitro.

Resistance Development

The development of resistance to Rifaximin (polymorphic form α) 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 travellers' diarrhoea was very low.
Clinical studies that investigated changes in the susceptibility of intestinal flora of subjects affected by travellers' 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 (polymorphic form α).
Development of resistance in the normal intestinal bacterial flora was investigated with repeated, high doses of rifaximin (polymorphic form α) in healthy volunteers and Inflammatory Bowel Disease patients. Strains resistant to rifaximin (polymorphic form α) 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 travellers' diarrhoea with rifaximin (polymorphic form α) of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitides* will not select for rifampicin resistance.

In general, the prevalence of acquired resistance may vary geographically and with time for selected species. Therefore, local information about on resistance is desirable, especially when treating severe infections. As with all antibiotics an expert should be consulted as necessary if the local tolerance is such that utility of Rifaximin (polymorphic form α) in at least some types of infections is questionable.

Susceptibility

Rifaximin (polymorphic form α) is a non-absorbed antibacterial agent. *In vitro* susceptibility testing cannot be used to reliably establish susceptibility or resistance of bacteria to rifaximin (polymorphic form α). There are currently insufficient data available to support the setting of a clinical breakpoint for susceptibility testing.

Rifaximin (polymorphic form α) has been evaluated in vitro on pathogens causing travellers' 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 (polymorphic form α). Due to the very low absorption from the gastro-intestinal tract rifaximin (polymorphic form α) is not clinically effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.

Topical Efficacy

The absorption of orally administered Rifaximin (polymorphic form α) by the gastrointestinal tract is negligible (less than 0.4 %). Therefore, the Rifaximin (polymorphic form α) is only locally active in the intestinal tract, where at the intake of the usual dosages, very high concentrations can be attained, which are significantly higher than the MICs (minimal inhibitors concentrations) for the tested enteropathogens (after 3 days of therapy with a daily dose of 800 mg, faecal concentrations of 4000-8000 µg/g faeces are attained).

Rifaximin (polymorphic form α) is thus able to efficiently combat the pathogen species existing in the gut.

Paediatric Use

The efficacy, posology and safety of Rifaximin (polymorphic form α) 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 (polymorphic form α). The large majority of enrolled children aged nore than 2 years. The characteristic which was present in all studies was diarrhoea of bacterial origin (proven before, during or after the treatment).

The data (the studies per se and a meta-analysis) show that there is a positive trend to demonstrate efficacy of Rifaximin (polymorphic form α) in a special condition (acute diarrhoeas (mainly recurrent or relapsing) which are known or supposed to be caused by non- invasive Rifaximin (polymorphic form α) 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 also Section 4.2).

Others

The broad antibacterial spectrum of Rifaximin (polymorphic form α) enables the efficient reduction of large amounts of gut bacteria. Because of this, also the bacterial production of ammonia and of other toxic substances involved in the pathogenesis and symptomatology of hepatoportal encephalopathy is reduced.

There are no indices for the induction of a necrotizing enterocolitis. Even if Mycobacterium tuberculosis is in-vitro sensitive against Rifaximin (polymorphic form α) after oral treatment, Rifaximin (polymorphic form α) has in-vivo practically no effect in the treatment of tuberculosis because of its missing systemic availability. For the same reason, the risk of the induction of a cross- resistance to Rifampicin is assessed as extremely low.

5.2 Pharmacokinetic Properties

Absorption

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration Rifaximinin the polymorph α form is virtually not absorbed (less than 0.4 %).

After repeated administration of therapeutic doses of Rifaximin (polymorphic form α) 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
Rifaximin (polymorphic form α) is excreted primarily unchanged in the faeces. The total amount of Rifaximin (polymorphic form α) which is excreted in urine, does not exceed 0.4 % of the administered dose.

Linearity/non-linearity
The rate and extent of systemic exposure of humans to Rifaximin (polymorphic form α) appeared to be characterized by non- linear (dose-dependent) kinetic which is consistent with the possibility of dissolution-rate-limited absorption of Rifaximin (polymorphic form α).

Special Population
No clinical data are available for the use of Rifaximin (polymorphic form α) in patients with renal dysfunctions.
Patients with hepatic encephalopathy show a higher systemic exposition than healthy volunteers. Due to the available safety data on Rifaximin (polymorphic form α) in patients with hepatic insufficiency and due to the local activity no specific dosage adjustment is recommended.

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 (polymorphic form α) during gestation, an increase in the incidence of skeletal variations was observed. The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL Data

6.1 Excipients

Tablet core:
Microcrystalline Cellulose
Glycerol Distearate

Sodium Starch Glycolate
Anhydrous Colloidal Silica
Talc

Tablet coating:
Hypromellose
Titanium Dioxide
Propylene Glycol
Red Iron Oxide E172
Disodium Edetate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4 Special Precautions for Storage

Store below 30°C

6.5 Nature and Contents of Container

Blister packs made of Transparent PVC/PE/PVDC-film aluminium foil in packs of 12, 24, 36 tablets.

6.6 Special Precautions for Disposal

No special requirements.

7. MANUFACTURER
ALFASIGMA S.P.A, Italy
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65020 - Alanno (PE),
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8. Licence Holder
Megapharm Ltd.
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9. Marketing Authorisation Number
149-55-33667

10. Revised in December 2024 according to MOHs guidelines.