

## **Product Specification**

### **Summary of Product Characteristics**

#### **1. NAME OF THE PHARMACEUTICAL PRODUCT**

**Lormyx 200 mg**

film-coated tablets

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 film-coated tablet contains: Rifaximin (polymorphic form  $\alpha$ ) 200 mg

See Section 6.1 for a complete list of all other ingredients.

#### **3. DOSAGE FORM**

Film-coated tablet

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

#### **4. CLINICAL INFORMATION**

##### **Indications:**

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

##### **4.2 Dosage, Type and Duration of Application**

###### Dosage

###### ***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  $\alpha$ ))
- *Non-complicated diverticular diseases, Hepatic encephalopathy:* 2 - 3 times per day 2 film-coated tablets Lormyx (corresponding to 800 - 1200 mg Rifaximin (polymorphic form  $\alpha$ )) per treatment cycle.

###### ***Children***

The safety and effectiveness of Rifaximin (polymorphic form  $\alpha$ ) 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.

###### Type of Application

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 Application

###### *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

Lormyx 200 mg - film-coated tablets must not be used: with known hypersensitivity to the active component Rifaximin (polymorphic form  $\alpha$ ) and other derivatives of Rifamycin as well as one of the other ingredients of the medicinal product.

#### 4.4 Particular warnings and precautionary measures concerning application

During longer treatment duration with high doses or with existing injuries of the intestinal mucosa, absorption of small amounts of Rifaximin (polymorphic form  $\alpha$ ) (less than 0.4 %) and slight reddening of the urine can occur. This is based on the colour of the active component which is red/orange like most Rifamycin antibiotics.

Due to the low absorption (see 5.2), Lormyx is not suitable for treatments of systemic infections or invasive infections of the intestinal mucosa. Using Rifaximin (polymorphic form  $\alpha$ ) for patients with complicated diarrhoea with fever and blood in the stool is not recommended. If the symptoms persist for longer than 24 to 48 hours, taking Lormyx should be discontinued and a change of therapy should be considered.

Using Rifaximin (polymorphic form  $\alpha$ ) for infections with involvement of *campylobacter jejuni*, *shigella spp.* or *salmonella spp.* has not been investigated sufficiently and can therefore not be recommended.

#### 4.5 Interaction with other pharmaceutical products and other interaction

As the absorption via the gastro-intestinal tract of Rifaximin (polymorphic form  $\alpha$ ) taken orally is negligible (< 0.4 %), no systemic interaction with other pharmaceutical products is assumed. Studies for clinical interaction with healthy test subjects with Rifaximin (polymorphic form  $\alpha$ ) and pharmaceutical products which are metabolised via human cytochrome P450 isoenzymes (e. g. CYP3A), showed that Rifaximin (polymorphic form  $\alpha$ ) (600 mg daily) does not significantly affect the pharmacokinetics of Midazolam and oral contraceptives (with the active ingredients ethinyl-estradiol and norgestimate). Therefore, interaction with pharmaceutical products which are metabolised via these isoenzymes is not expected.

Interaction studies for concurrent use of Lormyx with other pharmaceutical products which may be used for Travellers' Diarrhoea (e. g. Loperamide or activated carbon) do not exist. At the earliest, Lormyx may be taken 2 hours after application of activated carbon.

Note:

The underlying condition itself can affect the enterohepatic cycle of oestrogen through the modification of the intestinal flora. As a result, its plasma concentration can decrease and the contraceptive protection may be compromised. Considering additional alternative contraceptive measures is therefore advisable.

#### 4.6 Fertility, Pregnancy and Breastfeeding

*Women of child-bearing age / Contraception for men and women*

Due to the effects of Rifaximin (polymorphic form  $\alpha$ ) on the intestinal flora, there may be reduced effectiveness of oral contraceptives containing oestrogen after taking this tablet. Interactions to that effect, however, are not currently known. Nevertheless, considering additional alternative contraceptive measures is recommended, especially if the oestrogen content – as with the so-called 'micro pill' - lies below 50  $\mu\text{g}$  (see also Section 4.5 Interaction).

*Pregnancy and Breastfeeding*

There is insufficient data for humans about the safety of taking Rifaximin (polymorphic form  $\alpha$ ) during pregnancy and whilst breastfeeding. Studies with experiments on animals have not shown indications of direct or indirect effects detrimental to health with regards to reproduction toxicity (see Section 5.3). As a preventive measure, it is advisable nevertheless not to take Lormyx 200 mg film-coated tablets during pregnancy or whilst breastfeeding.

#### 4.7 Impact on driving and the ability to operate machinery

No studies have been carried out concerning the impact on driving and the ability to operate machinery.

#### 4.8 Side-effects

Side-effects which occurred during the treatment with Rifaximin (polymorphic form  $\alpha$ ), are largely easy to moderate and they subside in most cases by themselves without a modification of the dosage or interruption of treatment with Rifaximin (polymorphic form  $\alpha$ ).

The assessment of side-effects is based on the following frequency details:

Very common (>1/10)	common (>1/100,<1/10)
Occasional (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)
Very rare (< 1/10,000)	Not known (Frequency cannot be estimated based on available data)

The following side-effects occurred more often during the actual treatment with Rifaximin (polymorphic form  $\alpha$ ) than with a placebo. This list contains side-effects which may also occur as symptoms of the underlying condition which is being treated:

##### Infections and parasitic diseases

Very rare: Dysentery, infections of the upper respiratory tract

##### Diseases of the blood and the lymphatic system:

Very rare: Lymphocytosis, monocytosis, neutropenia

##### Diseases of the nervous system

Common: Head ache, dizziness

Very rare: Nightmares, migraine, sleeplessness

##### Diseases of the ear and the labyrinth

Very rare: Ear ache, tinnitus

##### Diseases of the gastro-intestinal tract

Very Common: Flatulence

Common: Urge to defecate, nausea

Occasional: Stomach ache

Very rare: Diarrhoea, dry throat, dry lips, hernia inguinalis, gum disorders

##### Diseases of the kidneys and the urinary tracts

Very rare: Choluria, dysuria, haematuria, polyuria, proteinuria

##### Skin diseases and diseases of the under-skin cellular tissue

Common: Exanthema, urticaria, probably as a sign of hypersensitivity

Very rare: Sunburn

##### General diseases and ailments at the point of administration:

Occasional: Tiredness, desire to urinate, reduced appetite, menstrual disorders, weight loss

##### Tests

Rare: Increased values of liver function, increased aspartate amino-transferase

#### 4.9 Overdose

Up to now, no cases of clinically relevant overdoses of Rifaximin (polymorphic form  $\alpha$ ) have become known. In clinical studies, doses of a maximum of 2400 mg/d (12 tablets/day) over 5 days have been applied without significant risk.

When taking higher doses, it is recommended carrying out gastric lavage and suitable supporting measures.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

*Pharmaco-therapeutic group: Intestinal antibiotics, antibiotics (Rifaximin (polymorphic form  $\alpha$ )); ATC-Code: A07AA11*

#### Mode of action

The pharmaceutical product Lormyx contains Rifaximin (polymorphic form  $\alpha$ ) [4-desoxy-4-methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamicin SV] in the polymorph form alfa (oc). Rifaximin (polymorphic form  $\alpha$ ) is a broad spectrum antibiotic drug. It is a semi-synthetic derivative of Rifamycin SV. Like other members of the Rifamycin antibiotics group, it connects irreversibly to the beta-sub unit of the bacterial RNA-polymerase which is dependent on DNA, and therefore blocks the bacterial RNA- and protein synthesis. Due to its irreversible connection with the enzyme, Rifaximin (polymorphic form  $\alpha$ ) has a bactericidal effect on sensitive bacteria.

The spectrum of the anti-microbial action of Rifaximin (polymorphic form  $\alpha$ ) is broad. It includes most bacteria (gram-negative and gram-positive, aerobe and anaerobe), which cause intestinal infections, as well as bacteria of the physiological intestinal flora of humans.

The local efficacy with negligibly low absorption from the gastro-intestinal tract is typical for Rifaximin (polymorphic form  $\alpha$ ) in its polymorph form.

In general, the frequency of resistance for certain species can vary in terms of geography and time. Therefore, local information about the resistance situation is desirable, especially when treating severe infections. As with all antibiotics, medical advice should be sought if local resistance occurs so often that the purpose of taking Rifaximin (polymorphic form  $\alpha$ ) for some types of infections seems at least doubtful.

#### Children

The efficacy, dosage and safety of Rifaximin (polymorphic form  $\alpha$ ) for children below the age of 12 have not been sufficiently proven.

Literature searches found 9 studies about the efficacy for the paediatric population which included 371 children, 233 of whom received Rifaximin (polymorphic form  $\alpha$ ). The majority of children involved was older than 2 years. The characteristic of all studies was diarrhoea with a bacterial origin (tested before, during or after the treatment).

Data (of the individual studies and meta-analyses) shows a positive trend concerning the efficacy of Rifaximin (polymorphic form  $\alpha$ ) under certain circumstances (acute diarrhoea (mainly recurring), caused by identified or assumed not invasive Rifaximin (polymorphic form  $\alpha$ )-sensitive bacteria such as Escherichia coli). The dosage used most often for children between 2 and 12 years of age in these limited studies with few patients was in a range of 20-30 mg/kg/day in 2 to 4 individual administrations (see also Section 4.2).

#### Effects on the normal intestinal flora

As research has shown, a treatment with Rifaximin (polymorphic form  $\alpha$ ) results in a reduction of aerobic and anaerobic bacteria in the physiological human intestinal flora by 90 to 99%. This effect is reversible on completion of the treatment. That means there is no permanent change in the balance of the physiological intestinal flora.

#### Resistance Development

The development of possible resistance towards Rifaximin (polymorphic form  $\alpha$ ) is initially based on a single-level modification of the bacterial RNA-polymerase which is dependent on DNA. This process significantly differs from resistance caused by plasmid which often occurs with amino glycoside antibiotics. Bacterial resistance towards Rifaximin (polymorphic form  $\alpha$ ) can occur. However, it is transient and of lower-ranking clinical significance due to the typically shorter application and the pronounced anti-bacterial efficacy which is based on the high concentration of the active agent in the colon and which leads to an almost complete elimination of the pathogenic strains.

There is no information regarding the development of clinically relevant, systemic resistance towards Rifaximin (polymorphic form  $\alpha$ ) and other Rifamycin-derivatives after a treatment with Rifaximin (polymorphic form  $\alpha$ ).

The risk of inducing cross resistance towards Rifampicin is estimated as very low (see below).

In general, the frequency of resistance for certain species can vary in terms of geography and time. Therefore, local information about the resistance situation is desirable, especially when treating severe infections. As with all antibiotics, medical advice should be sought if local resistance occurs so often that the purpose of taking Rifaximin (polymorphic form  $\alpha$ ) for some types of infections seems at least doubtful.

#### Topical Efficacy

Administered orally, the absorption of Rifaximin (polymorphic form  $\alpha$ ) via the gastro-intestinal tract is negligible (less than 0.4 %). Therefore, Rifaximin (polymorphic form  $\alpha$ ) only has an effect locally in the intestines where, on taking the usual dosage, very high concentrations can be reached which are significantly higher than the MICs (minimal inhibitors concentrations) for the tested entero-pathogenics (after 3 days therapy with a daily dosage of 800 mg, faecal concentrations of 4000-8000  $\mu\text{g/g}$  faeces are reached).

Based on the negligible resorption of Rifaximin (polymorphic form  $\alpha$ ) from the gastro-intestinal tract, the risk of systemic side-effects is low.

#### Miscellaneous

The broad antibacterial spectrum of Rifaximin (polymorphic form  $\alpha$ ) enables the efficient reduction of large amounts of bacteria living in the intestines. This also reduces the bacterial production of ammonia and other toxic substances which are involved in the pathogenesis and symptomatology of hepatportal encephalopathy in severe liver damage with limited detoxification activity.

There is no information regarding the induction of necrotised enterocolitis. Even though mycobacterium tuberculosis is sensitive towards Rifaximin (polymorphic form  $\alpha$ ) in-vitro, Rifaximin (polymorphic form  $\alpha$ ) taken orally has practically no in-vivo effect during the treatment of tuberculosis due to its lack of systemic availability. For the same reason, the risk of inducing cross resistance towards Rifampicin is estimated as very low.

## **5.2 Pharmacokinetic Properties**

#### Absorption

Pharmacokinetic studies with rats, dogs and humans have shown that the absorption of Rifaximin (polymorphic form  $\alpha$ ) on oral administration is below the limit of detection or negligibly low (less than 0.4 %).

Plasma levels after administration of therapeutic dosages of Rifaximin (polymorphic form  $\alpha$ ) are below the limit of detection (limit of detection < 0.5 - 2-ng/ml) or negligible (in most cases less than 10 ng/ml) in healthy voluntary test subjects as well as patients whose intestinal mucosa has been damaged by infections and ulcerations in connection with ulcerative colitis or Crohn's Disease.

Comparative pharmacokinetic studies have shown that other polymorph forms of Rifaximin (polymorphic form  $\alpha$ ) are absorbed much more than the a-form.

#### Distribution

Almost all of the orally administered dosage of Rifaximin (polymorphic form  $\alpha$ ) is available in the intestinal tract where it reaches very high concentrations (after a 3-day treatment with a daily dosage of 800 mg, faecal concentrations of 4000-8000 $\mu\text{g/g}$  are reached).

#### Metabolism

Rifaximin (polymorphic form  $\alpha$ ) is hardly metabolised at all.

#### Elimination

Rifaximin (polymorphic form  $\alpha$ ) is primarily excreted without modification via the faeces. The total amount of Rifaximin (polymorphic form  $\alpha$ ) which is excreted with the urine does not exceed 0.4 % of the administered dosage.

#### Bioavailability

Rifaximin (polymorphic form  $\alpha$ ) is not systemically available in a reproducible way and therefore not suitable for the treatment of systemic infections.

#### Particular Populations

There is no clinical data about the use of Rifaximin (polymorphic form  $\alpha$ ) for patients with kidney malfunction. Patients with hepatic encephalopathy developed medium plasma peak concentrations of 13.5 ng/ml Rifaximin (polymorphic form  $\alpha$ ) after administration of 800mg Rifaximin (polymorphic form  $\alpha$ ) three times a day for 7 days. After 7 days, the correction for recovery was less than 0.1% of the administered dose. Based on the low systemic resorption of Rifaximin (polymorphic form  $\alpha$ ), no specific dosage adjustment is recommended for patients with liver insufficiency.

### **5.3 Pre-clinical Safety Data**

In pharmacological tests for the safety of orally administered Rifaximin (polymorphic form  $\alpha$ ), no toxic impact could be detected because of the minimal systemic absorption, even with high doses.

#### Acute Toxicity

After oral application of Rifaximin (polymorphic form  $\alpha$ ) in rats, even the maximum of orally administered doses of up to 2000 mg/kg proved as not lethal. During oral application in mice, a dosage of 2000 mg/kg proved to be the lowest lethal dosage.

During intravenous application, the lowest lethal dose was 40mg/kg for rats and mice.

#### Chronic Toxicity

Studies of the chronic toxicity after oral administration have been carried out with various animal species. In a six month study with rats and a nine month study with dogs, the treatment with Rifaximin (polymorphic form  $\alpha$ ) was tolerated well. No toxicity in the target organs was detected.

#### Mutagenic and Tumorigenic Potential

Tests with Rifaximin (polymorphic form  $\alpha$ ) did not give any indication concerning a mutagenic potential.

#### Reproduction Toxicology

Possible impact of Rifaximin (polymorphic form  $\alpha$ ) on the reproductive function and the embryo-foetal and peri-/postnatal development was tested on rats and rabbits. Repeated oral administration of doses up to 300 mg/kg had no effect on the general reproductive function and fertility in male and female rats. These results were confirmed in teratological studies with rabbits and doses of up to 1000 mg/kg. The highest dose of Rifaximin (polymorphic form  $\alpha$ ) where there was no effect on the pre- and postnatal development of the offspring and growth, behaviour and the reproductive abilities of the F1 generation, was 300 mg/kg, the highest doses tested.

## **6. PHARMACEUTICAL INFORMATION**

### **6.1 List of Other Ingredients**

Sodium Starch Glycolate  
Glycerol Distearate  
Anhydrous Colloidal Silica  
Talc  
Microcrystalline Cellulose  
Hypromellose  
Titanium Dioxide  
Disodium Edetate  
Propylene Glycol  
Red Iron Oxide E172

### **6.2 Incompatibilities**

Not applicable

### **6.3 Storage Life**

3 years

### **6.4 Special Precautionary Measures for Storage**

Store below 30°C

### **6.5 Type and Contents of the Container**

Blister packs made of PVC-/al-film in packs of 12, 24, tablets

### **6.6 Special Precautionary Measures for Disposal**

No particular information

## **7. MANUFACTURER**

Alfa Wassermann S.P.A  
VIA Enrico Fermi,  
1 - 65020 Alanno (Pescara),  
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## **8. LICENCE HOLDER**

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**This leaflet was approved by the Israeli Ministry of health on December 2014**