ROEMMERS

**Summary of Product Characteristics**

## 1. NAME OF THE MEDICINAL PRODUCT

*ROGASTRIL PLUS*

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| | | |
|---|---|---|
| *Active substances*: | Cinitapride (as Cinitapride acid tartrate) | 1.00 mg |
| | Simethicone | 200.00 mg |
| *Excipients*: | Microcrystalline cellulose (Avicel PH 101) | 600.00 mg |
| | Tricalcium phosphate anhydrous | 468.63 mg |
| | Polyvinylpyrrolidone | 50.00 mg |
| | Colloidal silicon dioxide | 10.00 mg |
| | Croscarmellose sodium | 70.00 mg |

## 3. PHARMACEUTICAL FORM

Tablets

## 4. CLINICAL PARTICULARS

### 4.1) Therapeutic indications

**Rogastril Plus** combines the activity of Cinitapride, an antidyspeptic and gastroprokinetic agent and that of Simethicone, a chemically inert agent with antifoaming and antiflatulent activity.

**Rogastril Plus** is indicated for the treatment of dyspepsia due to mild to moderate gastrointestinal dysmotility. It is recommended as coadjuvant treatment of gastro-esophageal reflux in patients not responding appropriately to proton pump inhibitors as well as for the relief of flatulence and meteorism.

### 4.2) Posology and method of administration

**Rogastril Plus** tablets: Adults: Administer 1 tablet, 3 times daily, 15 minutes prior to each meal.

## 4.3) Contraindications

Known hypersensitivity to Cinitapride, Simethicone or to any component of the formula.

Patients who may be harmed by stimulation of gastric motility (hemorrhages, obstruction or perforation). Patients with history of tardive dyskinesia associated to the use of neuroleptics. Pregnancy and nursing. Children.

## 4.4) Special warnings and special precautions for use

WARNINGS:

During treatment, situations requiring special alertness should be avoided, such as driving vehicles or operating hazardous machines.

PRECAUTIONS:

It is recommended to administer **Rogastril Plus** cautiously to patients consuming alcoholic beverages or medicines with central nervous system depressant effect.

Elderly patients under prolonged treatment may develop tardive dyskinesia.

Although some in vitro studies performed using much higher concentrations of Cinitapride than the plasma levels found in clinics suggest that Cinitapride may prolong cardiac repolarization, in vivo studies in both, animals and humans, showed no effect on the electrocardiogram, particularly on the QT interval.

## 4.5) Interactions with other medicinal products and other forms of interaction

***Cinitapride:***

Stimulation of gastric emptying by Cinitapride may alter absorption of some pharmacologically active substances. Therefore, patients should inform their physician about treatment with other medicines.

*Phenothiazines and other dopaminergic antagonists:* Cinitapride may potentiate their effect in the central nervous system.

*Digoxin:* Cinitapride may reduce the effect of digoxin by reducing its absorption.

*Atropine-like anticholinergics and opioid analgesics:* These drugs may reduce the effects of Cinitapride on the digestive tract.

*Alcohol, tranquillizers, hypnotics or narcotics:* Their concomitant administration with **Rogastril Plus** may potentiate its sedative effects.

*Cytochrome CYP3A4 and cytochrome CYP2C8:* In vitro, Cinitapride is mainly metabolized via the cytochrome CYP3A4 (and to a lesser extent via the cytochrome CYP2C8). Therefore concomitant use, be it orally or parenterally, of significant inhibitors of these isoenzymes may alter its pharmacokinetics; examples of such drugs are:

- Azole antifungals such as ketoconazole, itraconazole, micomazole, and fluconazole
- HIV protease inhibitors, specially indinavir and ritonavir
- Macrolide antibiotics such as erythromycin, clarithromycin, or troleandomycin
- The antidepressant nefazodone

Anyway, a study carried out in humans with repeated doses of Cinitapride, administered either alone or in combination with ketoconazole, showed that pharmacokinetic interaction is not significant, since the mean values of the area under the curve for Cinitapride increased approximately 2 times (range: 0.9 - 4.3; C.I. 95%: 1.5 - 2.4).

***Simethicone:***

Simethicone is a chemically inert compound which is not absorbed at gastrointestinal level. No interactions for Simethicone have been described up to date.

**4.6) Use during pregnancy and lactation**

*Pregnancy:* There are no sufficiently controlled studies in pregnant women with the association of Cinitapride and Simethicone. Therefore administration of **Rogastril Plus** during pregnancy is not recommended.

*Nursing:* As there are no studies available concerning excretion of Cinitapride in human milk, **Rogastril Plus** should not be administered during nursing, unless it is strictly necessary and suspension of breastfeeding is decided.

**4.7) Effects on ability to drive and use machines**

Although clinical pharmacology studies performed with Cinitapride did not show somnolence or alterations in psychometric tests in subjects treated with recommended doses, some patients may experience a slight sedation or somnolence. Therefore, situations requiring special attention should be avoided during treatment with **Rogastril Plus**, such as driving vehicles or operating hazardous machines.

**4.8) Undesirable effects**

On rare occasions, extrapyramidal symptoms may appear with spasms in the face, neck and tongue muscles, which disappear following treatment discontinuation.

In the case of long-term use, elderly patients may develop tardive dyskinesia.

Very rarely skin reactions (rash, pruritus) or gynecomastia may occur. Exceptionally, angioedema.

No clinically significant adverse events were observed with the use of Simethicone.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1) Pharmacodynamic properties**

**Rogastril Plus,** due to its Cinitapride component is a gastroprokinetic orthopramide with marked procholinergic effect. It increases the release of serotonin by blocking presynaptic serotonin receptors which results in a greater

serotoninergic activity. Though discrete, its antidopaminergic activity contributes to the therapeutic effect.
Cinitapride accelerates gastric emptying time in patients with pathological delay of gastric emptying and improves clinical symptoms in patients with dyspepsia associated to slow gastric emptying and gastrointestinal transit delay.
Cinitapride reduces the number and duration of reflux episodes in patients with gastroesophageal reflux as well as the period with esophageal pH below 4, thus improving significantly the symptomatology of this disease. In this case, efficacy may be due not only to an increase in lower esophageal sphincter pressure but also to an improvement in gastric emptying.
Simethicone is a chemically inert agent without systemic effect with antifoaming and antiflatulent activity, which reduces surface tension of mucus and gas bubbles formed within the gastrointestinal tract facilitating their coalescence, thus relieving distension and meteorism.

**5.2) Pharmacokinetic properties**

After oral administration of Cinitapride, it is rapidly absorbed and reaches maximum plasma levels 2 hours after administration. It is metabolized in the liver (> 90%) via the cytochrome CYP3A4 and to a lesser extent via the cytochrome CYP2C8, showing an important first-pass effect.
Its elimination half-life is of about 3 to 5 hours during the first 8 hours after administration with a mean residence time above 15 hours from thereon, although with extremely low plasma levels. Elimination takes place mainly through the bile and to a much lesser extent through urine (< 7 %). No accumulation has been observed after repeated administration of Cinitapride.
Simethicone is a chemically inert compound which is not absorbed at gastrointestinal level. It is excreted unchanged through feces without any evidence of enterohepatic circulation.
SPECIAL POPULATIONS
*Pediatric use:* There are no well controlled studies regarding safety of the combination of Cinitapride and Simethicone in children and adolescents, therefore, its use is not recommended in these groups of age.
*Geriatric use:* In accordance with general considerations for elderly patients, **Rogastril Plus** should be administered with caution to these patients. In the case of long-term use, tardive dyskinesia may occur.

**5.3) Preclinical safety data**

Cinitapride has a very low toxicity and a high therapeutic index. Sub-chronic and chronic toxicity studies in rats and dogs showed no unexpected adverse events, thus confirming safety of Cinitapride even in long-term use. Reproduction and mutagenicity studies revealed no anomalies.
Simethicone is physiologically inert and considered to be non-toxic. Preclinical data revealed no hazard for humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1) List of excipients

Microcrystalline cellulose (Avicel PH 101)
Tricalcium phosphate anhydrous
Polyvinylpyrrolidone
Colloidal silicon dioxide
Croscarmellose sodium

### 6.2) Shelf life

24 months

### 6.3) Special precautions for storage

The product should be stored in a dry place at a temperature below 30°C.

### 6.4) Nature and contents of container

Aluminum/PVC Aclar blister packages, packed with the leaflet in lithographed cardboard boxes.

### 6.5) Instructions for use and handling

Keep out of the reach of children.
Keep in a dry place at temperature below 30°C.

## 7. PRESCRIPTION ONLY MEDICINAL PRODUCT

**Rogastril Plus** tablets should be dispensed only under prescription.

## 8. MARKETING AUTHORISATION HOLDER

**ROEMMERS S.A.I.C.F.**

## 9. MARKETING AUTHORISATION NUMBER

Certificate N° 55,835

## 10. NAME AND ADDRESS OF THE MANUFACTURER

**ROEMMERS S.A.I.C.F.**
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