SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANTOPRAZOLE FRILAB 40 mg, powder and solvent for solution for injection (IV)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pantoprazole Sodium USP, equivalent to
Pantoprazole……...40 mg
For one bottle.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
Powder that is almost white or white.
NaCl solution , the pH is approximately 10 and the osmolality is approximately 382 mOsm/kg.
NaCl solution or 5% glucose solution, the pH is approximately 9 and 8.5 respectively.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Gastric and duodenal ulcers.
- Esophagitis due to gastroesophageal reflux.
- Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

4.2. Posology and method of administration

This medication must be administered by a healthcare professional and under appropriate medical supervision.
Intravenous administration of pantoprazole is recommended only when oral administration is not possible. Data are available on the intravenous use of pantoprazole for up to 7 days. Therefore, as soon as oral treatment is possible, intravenous administration of pantoprazole should be discontinued and replaced with oral administration of 40 mg of pantoprazole.

Recommended posology:
Gastric and duodenal ulcers, esophagitis due to gastroesophageal reflux
The recommended intravenous dose is one vial of pantoprazole (40 mg) per day.
Zollinger-Ellison syndrome and other pathological hypersecretory conditions .
For the long-term treatment of Zollinger-Ellison syndrome and other pathological hypersecretory conditions , the initial dose is 80 mg of pantoprazole daily. This may be increased or decreased as needed, based on the results of acid output measurements. If the dose exceeds 80 mg/day, it should be divided into two administrations. A temporary increase in dosage above 160 mg of pantoprazole daily is possible, but should not exceed the duration necessary to control acid secretion.
If rapid control of acid secretion is required, an initial dose of 2 x 80 mg of pantoprazole intravenously is sufficient to achieve a reduction in acid production to the target range (<10 mEq/h) within one hour for the majority of patients .

Special populations
Pediatric population:
Clinical experience in children is limited. Therefore, intravenous administration of pantoprazole is not recommended in patients under 18 years of age until further data are available.
Liver failure:
The maximum daily dose of 20 mg of pantoprazole (half of a 40 mg bottle) should not be exceeded in patients with severe hepatic impairment.
Kidney failure:
No dose adjustment is necessary in patients with renal insufficiency.
elderly patients
No dose adjustment is necessary in elderly patients

Method of administration:
Dissolve the powder by injecting 10 ml of 9 mg/ml (0.9%) sodium chloride injection solution into the lyophilized vial. For preparation instructions, see section 6.6.
The reconstituted solution can be administered directly, or diluted in 100 ml of 9 mg/ml (0.9%) sodium chloride solution, or 55 mg/ml (5%) glucose injection solution.
The solution must be used within 12 hours of preparation (See section 6.3).

The medication should be administered intravenously over 2 to 15 minutes.

4.3. Contraindications

Known hypersensitivity to pantoprazole, substituted benzimidazoles, or any of the excipients mentioned in section 6.1.

4.4. Special warnings and precautions for use

In case of alarming symptoms
In the presence of any alarming symptoms (e.g., significant involuntary weight loss, recurrent vomiting, dysphagia, hematemesis, anemia or melena) and in case of suspicion or presence of a gastric ulcer, a malignant condition must be ruled out because taking pantoprazole can alleviate symptoms and therefore delay diagnosis.
Further investigations should be considered if symptoms persist despite the administration of appropriate treatment.
Liver failure
In patients with severe hepatic impairment, liver enzyme levels should be monitored regularly during treatment. If these levels rise, treatment should be discontinued (see section 4.2).
Concomitant use of atazanavir
Concomitant administration of atazanavir with a proton pump inhibitor is not recommended (see section 4.5). If the combination of atazanavir and a proton pump inhibitor is considered essential, regular clinical monitoring is recommended, along with an increase in the atazanavir dose to 400 mg per 100 mg of ritonavir. The maximum recommended daily dose of pantoprazole is 20 mg.

Gastrointestinal infections of bacterial origin
Like all proton pump inhibitors, pantoprazole can promote the growth of intragastric bacteria. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections of bacterial origin (e.g., by *Salmonella* and *Campylobacter*).

4.5. Interactions with other medications and other forms of interaction

Effect of pantoprazole on the absorption of other drugs
Due to prolonged inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs whose bioavailability depends on gastric pH, such as certain azole antifungals (ketoconazole , itraconazole , posaconazole) and other drugs such as erlotinib .
+ Antiretroviral treatment (atazanavir)
Concomitant administration of atazanavir and other anti-HIV drugs whose absorption is pH-dependent with proton pump inhibitors may result in a substantial decrease in plasma concentrations of anti-HIV drugs and impact the effectiveness of these treatments.
concomitant administration of atazanavir and proton pump inhibitors is not recommended. (See section 4.4.)
+ Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interactions were observed during concomitant administration of proton pump inhibitors and phenprocoumon or warfarin in pharmacokinetic studies, isolated cases of INR (International Normalized Ratio) changes have been reported during post-marketing concomitant treatment. Therefore, monitoring of prothrombin time/INR is recommended.
patients treated with coumarin anticoagulants (such as phenprocoumon or warfarin), at the start and end of treatment, or in case of intermittent administration of pantoprazole.
Studies on other drug interactions
Pantoprazole is extensively metabolized in the liver by the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19, and other metabolic pathways include oxidation by CYP3A4.
No clinically significant interactions were observed in specific studies including those involving carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive composed of levonorgestrel and ethinylestradiol .
Results from various interaction studies show that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (caffeine, theophylline), by CYP2C9 (piroxicam , diclofenac , naproxen), by CYP2D6 (metoprolol), by CYP2E1 (ethanol) and does not interfere with the role of P-glycoprotein in the absorption of digoxin.
There are no interactions with antacids administered concomitantly.
Interaction studies have been conducted on the concomitant administration of pantoprazole and various antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were observed.

4.6. Pregnancy and breastfeeding

Pregnancy:
There is very limited data on the use of pantopazole in pregnant women. In animal reproduction studies, signs of fetotoxicity were observed (see section 5.3). The potential risk in humans is unknown. Therefore, pantoprazole should only be administered during pregnancy if clearly needed.

Breastfeeding:

Animal studies have shown that pantoprazole is excreted in breast milk. Excretion in human breast milk has also been reported. Therefore, the decision to continue/discontinue breastfeeding or to continue/discontinue pantoprazole therapy should be made taking into account the benefit of breastfeeding for the child and the benefit of pantoprazole therapy for the mother.

4.7. Effects on the ability to drive vehicles and use machinery

Side effects, such as dizziness or visual disturbances, may occur (see section 4.8).
Patients experiencing this type of side effect should not drive vehicles or operate machinery.

4.8. Undesirable effects

Approximately 5% of patients are likely to experience adverse reactions (ARs). The most frequently reported adverse reactions are diarrhea and headache, both occurring in approximately 1% of patients.

Severe allergic reactions (rare) : swelling of the tongue and/or throat, difficulty swallowing, skin rash (hives), difficulty breathing, allergic-type facial swelling (Quincke's edema), severe dizziness with increased heart rate and profuse sweating.

Serious skin disorders (frequency not known): blisters on the skin and rapid worsening of the general condition, erosion (including slight bleeding) of the eyes, nose, mouth/lips or genitals (Stevens-Johnson syndrome, Lyell's syndrome, erythema multiforme) and sensitivity to light.

Other serious side effects (frequency not known): yellowing of the skin and whites of the eyes (severe liver cell damage, jaundice), or fever, rash, enlarged kidneys sometimes with pain when urinating and/or in the lower back (severe kidney inflammation).

Other side effects include:
- **Frequent (** affecting between 1 and 10 users out of 100)
Inflammation of the vein wall and blood clots (thrombophlebitis) at the injection site.
- **Infrequent** (affecting between 1 and 10 users out of 1,000)
Headache, dizziness, diarrhea, lightheadedness, vomiting, bloating and flatulence (gas), constipation, dry mouth, abdominal pain and discomfort, skin rash, exanthem, rash, tingling, feeling of weakness, fatigue and general malaise, sleep disturbances.
- **Rare** (affecting between 1 and 10 users out of 10,000)
Visual disturbances such as blurred vision, hives, joint pain, muscle pain, weight changes, increased body temperature, swelling of the limbs (peripheral edema), allergic reactions, depression, increased breast size in men.
- **Very rare** (affecting less than 1 in 10,000 users)
Disorientation
- **Frequency not known** (frequency cannot be estimated from the available data)
Hallucinations, confusion (especially in patients with a history of these symptoms), decreased blood sodium levels.

Taking Pantoprazole FRILAB for more than three months may cause a decrease in magnesium levels. Low magnesium levels can lead to fatigue, involuntary muscle contractions, disorientation, seizures, dizziness, and an increased heart rate. A low magnesium level can also lead to a decrease in potassium and calcium levels in the blood.

Prolonged use of proton pump inhibitors such as Pantoprazole FRILAB, particularly for more than one year, increases the risk of suffering a fracture of the hip, wrist or spine.

Side effects identified through blood analysis:
- **Infrequent** (affecting between 1 and 10 users out of 1,000):
Elevated liver enzyme levels
- **Rare** (affecting between 1 and 10 users out of 10,000) :
Increased bilirubin, increased blood fats
- **Very rare** (affecting less than 1 in 10,000 users):
A decrease in the number of platelets can lead to an increased number of bleeds and bruises compared to normal; a reduction in the number of white blood cells can lead to an increased frequency of infections.

4.9. Overdose

No symptoms of overdose have been reported in humans.
Systemic exposure to up to 240 mg of pantoprazole administered intravenously over 2 minutes was well tolerated. Because pantoprazole is highly protein-bound, it is not readily dialyzable. In the event of an overdose associated with clinical signs of intoxication, no specific therapeutic recommendations can be given other than symptomatic and supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: **PROTON PUMP INHIBITORS** , ATC code: **A02BC02**

Mechanism of action
Pantoprazole is a substituted benzimidazole that inhibits the secretion of hydrochloric acid in the stomach by specifically blocking the proton pump of the gastric parietal cell.

Pantoprazole is converted into its active form in the acidic environment of the parietal cells, where it inhibits the H^+/K^+ -ATPase proton pump, the final stage of hydrochloric acid production in the stomach. This inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, symptom relief is achieved within two weeks. As with other proton pump inhibitors and H2 receptor antagonists, pantoprazole treatment reduces stomach acidity, leading to a proportional increase in gastrin levels. This increase in gastrin is reversible. Because pantoprazole binds to the distal enzyme at the cell receptor, it can inhibit hydrochloric acid secretion regardless of the stimulus (acetylcholine, histamine, or gastrin). The effect is the same whether the product is administered orally or intravenously.
gastrin levels increase with pantoprazole. In most cases, during short-term treatment, they do not exceed the upper limits of normal. These values most often double during long-term treatment. However, excessive increases have only been reported in isolated cases. Consequently, a mild to moderate increase in the number of endocrine-specific cells (ECLs) in the stomach is observed in a minority of cases during prolonged treatment (similar to adenomatoid hyperplasia). However, according to studies conducted to date, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as described in animals has not been observed in humans (see section 5.3).
Based on the results of studies conducted on animals, an effect on the endocrine parameters of the thyroid cannot be excluded during prolonged treatment (more than one year) with pantoprazole.

5.2. Pharmacokinetic properties

General pharmacokinetic data
Pharmacokinetic data remain constant after single or repeated administration. For administered doses ranging from 10 to 80 mg, the plasma kinetics of pantoprazole are linear after oral and intravenous administration.

Distribution
Pantoprazole is 98% bound to plasma proteins. The volume of distribution is 0.15l/kg.

Elimination
The substance is almost exclusively metabolized by the liver. The main metabolic pathway is demethylation by CYP2C19, followed by sulfation; other metabolic pathways include oxidation by CYP3A4 at approximately 0.1 L/h/kg. Cases of delayed elimination are rare. Since specific activation occurs in the gastric parietal cell, there is no correlation between the plasma elimination half-life and the duration of action of the product. Renal elimination is the main route of elimination for pantoprazole metabolites (approximately 80%), with the remainder eliminated in the feces. The main metabolite found in plasma and urine is desmethylpantoprazole , in its sulfation conjugate form . The half-life of the main metabolite (approximately 1.5 hours) is no longer than that of pantoprazole.

Characteristics in certain specific patients/populations:
Approximately 3% of the European population lacks a functional CYP2C19 enzyme and are referred to as poor metabolizers. In these individuals, pantoprazole is likely metabolized primarily by the CYP3A4 enzyme. Following administration of a single 40 mg dose of pantoprazole, the mean area under the plasma concentration-time curve (AUC) is approximately six times greater in poor metabolizers than in subjects with a functional CYP2C19 enzyme (extensive metabolizers). Peak mean plasma concentrations are increased by 60%. These findings have no impact on pantoprazole dosage.
No dose reduction is necessary when administering pantoprazole to patients with renal impairment (including dialysis patients). As in healthy subjects, the elimination half-life of pantoprazole is short. Only very small amounts of pantoprazole are removed by dialysis.
Although the main metabolite has a slightly longer half-life (2-3 h), excretion remains rapid and therefore no accumulation is observed.
In cirrhotic patients (Child classes A and B), despite the prolongation of the half-life to 7 to 9 h and the increase in AUC by a factor of 5 to 7, the maximum plasma concentration is only slightly increased (x 1.5) compared to healthy subjects. The slight increase in AUC and Cmax observed in the elderly compared to the young has no clinical significance.
Children
Following intravenous administration of a single dose of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2 to 16 years, no significant correlation was observed between clearance and age or weight. The AUC and volume of distribution were consistent with data observed in adults.

5.3. Preclinical safety data

Preclinical data do not highlight any particular risk in humans, based on pharmacological safety, repeated dose toxicity and genotoxicity studies.

In 2-year carcinogenicity studies in rats, neuroendocrine neoplasms were observed. In addition, squamous cell papillomas were observed in the foregut of the rat stomach. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been thoroughly investigated, and it can be concluded that this is a secondary reaction to the massive increase in gastrin levels in treated rats. In 2-year studies in rodents, an increased number of liver tumors was observed in female rats and mice and was interpreted as being related to the high rate of hepatic metabolism of pantoprazole.
A slight increase in thyroid neoplastic transformations was observed in the group of rats receiving the highest dose (200 mg/kg). The development of these neoplasms is associated with pantoprazole-induced changes in hepatic thyroxine degradation in rats. Since the therapeutic dose in humans is low, no adverse effects on the thyroid gland are expected.
In animal reproduction studies, slight signs of fetotoxicity were observed at doses above 5 mg/kg. Research showed no effect on fertility or teratogenicity.
Placental transfer has been studied in rats and it has been shown to increase with the progression of gestation. Consequently, the concentration of pantoprazole in the fetus is briefly elevated before birth.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The active substance is pantoprazole. Each bottle contains 40 mg of pantoprazole (as sodium sesquihydrate).
The other components (excipients) are: sodium citrate dihydrate , non-pyrogenic mannitol and sodium hydroxide.

6.2. Incompatibilities

This medicine should not be mixed with other medicines except those mentioned in section 6.6

6.3. Shelf life

Before reconstitution: 24 months.
After reconstitution or reconstitution and dilution, physico-chemical stability has been demonstrated for 12 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, the storage time and conditions prior to use are the responsibility of the user.

6.4. Special precautions for storage

Keep the bottle in the outer carton, protected from light and at a temperature below 30°C.
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5. Nature and contents of container

Combipack containing 1 vial of lyophilized powder and 1 ampoule of 10 ml NaCl USP 0.9% w/v

6.6. Special precautions for disposal and handling

A ready-to-use intravenous solution is prepared by injecting 10 mL of 9 mg/mL (0.9%) sodium chloride solution containing the lyophilized powder into the lyophilized vial. The reconstituted solution should be clear and colorless. The solution can be administered either directly or after being mixed with 100 mL of 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL glucose injection. Glass or plastic containers should be used for dilution.
Only the solvents mentioned should be used for the preparation or mixing of PANTOPRAZOLE 40 mg, powder for solution for injection.
The medication should be administered intravenously over 2 to 15 minutes.

7. OPERATORS AND MANUFACTURERS

Operator of the export marketing authorization
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8. DATE OF REVISION OF THE TEXT

28 July 2022.

9. DOSIMETRY

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

Prescription-only medicine.