SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG
Pantoprazole Frilab 40 mg powder for injection solution (IV).

2. Qualitative and quantitative composition

Pantoprazole .... .40 mg
(In the form of sodium sesquihydrate)
For a bottle.
excipients:
Each powder vial contains 5 mg of sodium citrate dihydrate and sodium hydroxide qs.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection.
White or almost white powder.
For the reconstituted solution with 10 ml NaCl 0.9% solution, the pH is about 10 and the osmolality about 382 mOsm / kg.
For the reconstituted solution with the addition of 100 ml of NaCl 0.9% or 5% glucose solution, the pH is respectively about 9 or 8.5.

4. CLINICAL DATA

4.1. Therapeutic indications
- gastric and duodenal ulcers.
- gastroesophageal reflux.
- Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

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

Recommended dosage:
Gastric and duodenal ulcers, gastroesophageal reflux disease
Intravenous recommended dose is a vial of pantoprazole (40 mg) per day.
Zollinger-Ellison syndrome and other pathological hypersecretory conditions.
Under long-term treatment of Zollinger-Ellison syndrome and other pathological hypersecretory conditions, the starting dose is 80 mg pantoprazole daily. This can be increased or decreased as needed, depending on the results of the acid flow measurements. In the case of greater than 80 mg / day dose, the dose should be divided into two administrations. A temporary increase in the dose above 160 mg pantoprazole daily is possible but should not exceed the time required for the control of acid secretion.
If a rapid control of acid secretion is required, a starting dose of 2 x 80 mg pantoprazole intravenously is sufficient to achieve a decrease of acid production in the target range (<10 mEq / h) in a period of an 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 until further data are available.
Hepatic insufficiency :
The maximum daily dose of 20 mg pantoprazole (half a vial of 40 mg) should not be exceeded in patients with severe liver failure.
Renal failure :
No dose adjustment is necessary in renal impairment.
No dose adjustment is necessary in the elderly

Administration mode :
Dissolve the powder by injecting into the vial of lyophilisate 10 ml of injectable solution of sodium chloride 9 mg / ml (0.9%). For preparation instructions or 6.6.
The reconstituted solution may be administered directly, or diluted in 100 ml sodium chloride 9 mg / ml (0.9%), or injectable glucose solution 55 mg / ml (5%).
The solution should be used within 12 hours of preparation (see section 6.3.).
The drug should be administered intravenously over 2 to 15 minutes.

4.3 Contraindications

Known hypersensitivity to pantoprazole, substituted benzimidazoles, or any of the excipients.

4.4 Special warnings and precautions

If alarming symptoms
In the presence of any alarming symptom (eg significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anemia or melaena) and in case of suspicion or presence of gastric ulcer, malignancy should be excluded as taking pantoprazole may alleviate symptoms and therefore delay diagnosis.
Additional tests should be considered if symptoms persist despite administration of appropriate treatment.
Hepatic insufficiency
In patients with severe hepatic impairment, an assessment of liver enzymes should be carried out regularly during treatment. If elevations thereof, treatment should be discontinued (see section 4.2).
Concomitant use of atazanavir
Co-administration of atazanavir with a proton-pump inhibitor is not recommended (see section 4.5). If the combination of atazanavir with a proton-pump inhibitor is judged unavoidable, clinical monitoring regular is recommended associated with an increase in the dose of atazanavir to 400 mg with 100 mg ritonavir. The maximum recommended daily dose of pantoprazole is 20 mg.

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

4.5 Interaction with other drugs 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 the drug whose bioavailability is dependent on the 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 HIV medications whose absorption is pH-dependent with inhibitors of proton pump can result in a substantial decrease in plasma levels of anti-HIV drugs and have an impact on the effectiveness of these treatments.
Concomitant administration of atazanavir and proton pump inhibitors is not recommended. (See section 4.4.)
+ Coumarin Anticoagulants (warfarin or phenprocoumon)

Although no interactions have been observed during simultaneous administration of inhibitors of proton pump and phenprocoumon or warfarin during pharmacokinetic studies, isolated cases of changes in INR (International Normalized Ratio) were reported in a concomitant treatment, after marketing. Therefore, it is recommended to monitor the prothrombin time / INR
patients treated with coumarin anticoagulants (such as warfarin or phenprocoumon), at the start and discontinuation of treatment, or during irregular use 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 carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl estradiol.
Results from various studies on interactions demonstrate that pantoprazole does not affect the metabolism of active substances metabolised 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 concomitantly administered antacids.
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 lactation

Pregnancy :

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

Breast-feeding:

Studies in animals have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, the decision to continue / discontinue breastfeeding or to continue / discontinue therapy with pantoprazole should be made taking into account the benefit of breast feeding for the child and pantoprazole treatment of benefit to the mother.

4.7 Effects on ability to drive and use machines

Side effects such as dizziness or blurred vision, may occur (see rubrique4.8).

Patients with this type of adverse reaction should not drive or operate machinery.

4.8Effetsindésirables

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

Serious allergic reactions (rare): Swelling of the tongue and / or throat, difficulty swallowing, rash (urticaria), trouble breathing, swelling of allergic-type face (angioedema), severe dizziness with increased heart and heavy sweating rate.

severe skin disorders (frequency unknown): blisters on the skin and rapid deterioration of general condition, erosion (including slight bleeding) of eyes, nose, mouth / lips or genitals (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) and sensitivity to light.

Other serious reactions (frequency not known): yellowing of the skin and whites of the eyes (severe liver cell injury, jaundice), or fever, rash, enlarged kidneys sometimes pain during urination and / or in the lower back (renal inflammation serious).

Other side effects are:
- Common (affects between 1 and 10 users 100)
Inflammation of the lining of the vein and blood clots (thrombophlebitis) at the injection site.
- Uncommon (affects 1 to 10 users in 1000)
Headache, dizziness, diarrhea, dizziness, vomiting, bloating and flatulence (gas), constipation, dry mouth, pain and discomfort in the abdomen, rash, rash, rash, tingling, feeling of weakness, fatigue and malaise generally, sleep disorders.
- Rare (affects between 1 and 10 users in 10,000)
Vision problems such as blurred vision, hives, joint pain, muscle pain, weight changes, increased body temperature, swelling of the limbs (peripheral edema), allergic reactions, depression, enlarged breasts in men.
- Very rare (affecting less than 1 user in 10,000)
disorientation
- Not known (frequency can not be estimated from the available data)
Hallucinations, confusion (especially in patients with a history of these symptoms); decreased sodium levels in the blood.

A take of 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, convulsions, dizziness and increased heart rate. A low magnesium levels can also cause a decrease in potassium and calcium levels in the blood.

Prolonged use of the proton pump inhibitors such as pantoprazole FRILAB, especially for a period exceeding one year, increases the risk of fracture of the hip, wrist or spine.

Side effects identified through blood tests:
- Uncommon (affects 1 to 10 users in 1000):
Elevated liver enzyme levels
- Rare (affects 1 to 10 users in 10,000):
Increased bilirubin, increased fat in the blood
- Very rare (affecting less than 1 user in 10 000):
Decrease the number of platelets may result in an increased number of bleeding and hematoma compared to normal, reduction of white blood cells can result in increased frequency of infections.

4.9Surdosage
No symptoms of overdose have been reported in humans.

Systemic exposures up to 240 mg pantoprazole administered intravenously over 2 minutes were well tolerated. As pantoprazole is highly protein bound, it is not readily dialysable. In case of overdose associated with clinical signs of intoxication, no specific therapeutic recommendations can be given with the exception of symptomatic and supportive treatment.

5.PROPRIETESPHARMACOLOGIQUES
5.1 Pharmacodynamic properties

Pharmacotherapeutic: PUMP INHIBITORS PROTON, ATC code: A02BC02.

Action mechanism
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the gastric parietal cell proton pump acid.

Pantoprazole is converted in active form in the acidic environment of the parietal cells in which it inhibits the proton pump H + / K + -ATPase, that is to say the final stage of production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal acid secretion and stimulated acid secretion. In most patients, symptoms disappear is obtained in two weeks. As with

other proton pump inhibitors and other H2 antagonists, treatment with pantoprazole reduced acidity in the stomach and thus results in increased gastrin levels proportional to the reduction in acidity. The increase in gastrin is reversible. Because pantoprazole binds to the distal enzyme at the cell receptor, it can inhibit the secretion of hydrochloric acid regardless of the nature of the stimulus (acetylcholine, histamine, gastrin). The effect is the same, the product is administered orally or intravenously.

The gastrinemia increases under pantoprazole if fasting. In most cases, during treatment of short duration gastrinemia does not exceed the upper limits of normal. These values double in most cases during long-term treatment. However, an excessive increase is reported only in isolated cases. Therefore, a slight to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (similar to a hyperplasieadénomatoïde). However, according to studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoid as described in animals has not been observed in humans (see section 5.3.).

According to the results of studies conducted on animals, we can not rule out an effect on endocrine parameters of the thyroid during prolonged treatment (over one year) with pantoprazole.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pharmacokinetic data remain constant after single or repeated administration. For doses varying from 10 to 80 mg, the plasma kinetics of pantoprazole is linear after both oral and intravenous administration.

Distribution

Binding of pantoprazole to plasma protein is 98%. The distribution volume is 0.15L / kg.

Elimination

The substance is almost exclusively metabolized by the liver. The main metabolic pathway is ladéméthylation by the CYP2C19 followed by sulfation; the other metabolic pathways include oxidation by CYP3A4 about 0.1l/h/kg

Cases of patients with delayed elimination are few. Since the specific activation takes place in the gastric parietal cell, there is no correlation between the plasma half-life of elimination and product duration of action.
Renal excretion is the major route of elimination of metabolites of pantoprazole (about 80%), the rest being excreted in the feces. The main metabolite in plasma and urine is desmethylpantoprazole sulfate conjugate form. The half-life of the main metabolite (about 1.5 hours) is not greater than that of pantoprazole.
Features some patients / special populations:
About 3% of the European population does not have a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly by the enzyme CYP3A4. After administration of a single dose of 40 mg pantoprazole, the mean area under the curve of plasma concentration vs. time is about 6 times larger in poor metabolizers than in subjects bearing a functional CYP2C19 enzyme (extensive metabolisers fast). The peak mean plasma concentrations are increased by 60%. This data does not affect the dose of pantoprazole.
No dose reduction is required in the administration of pantoprazole to patients with renal insufficiency (including dialysis patients). As in healthy subjects, half life of pantoprazole elimination is short. Only very small amounts of pantoprazole are dialyzed.
Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation is not observed.
In patients with cirrhosis (classes A and B according to Child), despite the increase in half-life up to 7 to 9 am and the increase in AUC by a factor of 5 to 7, the maximum plasma concentration n is only slightly increased (x 1.5) compared with healthy subjects.
The slight increase in AUC and Cmax in elderly compared with younger was not clinically relevant.
Children
Following intravenous administration of a single dose of 0.8 or 1.6 mg / kg pantoprazole to children aged 2 to 16 years, no significant correlation between clearance and age or weight were observed. The AUC and volume of distribution were consistent with the data observed in adults.
5.3 Preclinical Safety Records

Preclinical data reveal no particular hazard for humans, given the pharmacological safety testing, repeated dose toxicity, and genotoxicity.
In the carcinogenicity studies of 2 years in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism causing the formation of gastric carcinoids by substituted benzimidazoles has been studied extensively and we can conclude that it is a secondary reaction to the massively elevated serum gastrin in rats during treatment . During the 2 years studies in rodents, an increased number of liver tumors was observed in rats and female mice and was interpreted as related to the high rate of hepatic metabolism of pantoprazole.
A slight increase in neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg / kg). The occurrence of these neoplasms is associated with pantoprazole-induced changes in the breakdown of thyroxine in the liver in rats. The therapeutic human dose is low, no adverse effect on the thyroid gland is awaited

In reproduction studies in animals, signs of slight fetotoxicity were observed at doses above 5 mg / kg. Research showed no effect on fertility or teratogenic effect.
Placental transfer has been studied in rats and it was highlighted that increased with advancing gestation. As a result, concentration of pantoprazole in the fetus is increased shortly before birth.

6. PHARMACEUTICAL DATA

6.1. List of excipients
The active substance is pantoprazole. Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate).
The other ingredients (excipients) are sodium citrate dihydrate, apyrogenic mannitol and sodium hydroxide.

6.2. incompatibility
This drug should not be mixed with other medicinal products except those mentioned in section 6.6

6.3. Shelf life
Before reconstitution: 24 months.
After reconstitution or reconstitution and dilution, the physicochemical stability has been demonstrated for 12 hours at 25 ° C.
From a microbiological point of view, the product should be used immediately. If not used immediately, storage life and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Store at a temperature not exceeding 25 ° C.
Keep the vial in the package in order to protect from light.
For storage conditions of the reconstituted and diluted medicinal, see section 6.3.

6.5. Nature and contents of container
clear glass bottle of 12 ml, Type I, closed with chlorobutyl stopper and an aluminum cap, containing 40 mg of powder for injection.

6.6. Special precautions for disposal and handling
Preparing an intravenous solution ready for use by injecting into the vial of lyophilisate 10 ml sodium chloride 9 mg / ml (0.9%) containing the lyophilized powder. The reconstituted solution should be clear and colorless. The solution can either be administered directly or after mixing in 100 ml of an injectable solution of sodium chloride 9 mg / ml (0.9%) or injectable glucose solution 50 mg / ml (5%). glass or plastic containers to be used for dilution.
Only the solvents mentioned should be used for the preparation or mixture Pantoprazole 40 mg powder for solution for injection.

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

7. HOLDER and OPERATOR

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9. DOSIMETRY
Not applicable.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Not applicable.

CONDITIONS OF PRESCRIPTION AND DELIVERY

Medicinal product subject to medical prescription.