VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pantoprazole 40 mg powder for solution for injection is a medicine used to treat reflux oesophagitis, gastric and duodenal ulcer, Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions. All these conditions require inhibition of acid secretion, which is reached using an antisecretory agent like pantoprazole.

The frequency estimates of gastric reflux oesophagitis[i] range from 8.8% to 25.9% in Europe. Additionally, frequency estimates for all geographic areas except East Asia are in the approximate 10%–20% range. Gastric reflux oesophagitis is considered to be a frequent disease worldwide having, as a result, potentially serious societal consequences, since the pain and discomfort caused by this condition adversely impacts many aspects of patients' lives (including their productivity at work). Gastric reflux oesophagitis is also a risk factor for the development of more serious conditions. There are also still few data regarding the frequency of gastric reflux oesophagitis in paediatric populations, and few studies of the disease incidence.

Peptic ulcer disease (gastric and duodenal ulcer) is still highly associated with infection related to H. pylori bacteria in southern Europe. Only 1.6% of all duodenal ulcers and 4.1% of all gastric ulcers were not associated with either H. pylori infection or medicine use (nonsteroidal anti-inflammatory drugs)ii. An infected individual has an estimated lifetime risk of 10-20% for the development of peptic ulcer disease, which is at least 3-4 fold higher than in non-infected subjects. H. pylori infection can be diagnosed in 90-100% of duodenal ulcer patients and in 60-100% of gastric ulcer patients. Factors that may influence the peptic ulcer risk in infected subjects are the amount of gastric acid production (which is increased in duodenal ulcer disease and decreased ingastric ulcer disease), the presence of abnormal change in the nature of the gastric tissue (metaplasia) in the duodenal bulb, smoking, and genetic factorsiii. In the United States about four million people have active peptic ulcers and about 350,000 new cases are diagnosed each yeariv.

The true incidence of Zollinger-Ellison syndrome is not known. It is considered a rare disease and constitutes 0.1% or more of cases of peptic ulcer disease. The frequency of Zollinger-Ellison syndrome in Europe was estimated to be of 5,3/100000 patients[v]. Risk factors that increase the chance of getting Zollinger-Ellison syndrome include history of endocrine disorders, recurrent peptic ulcers and having family members with a genetic disorder called multiple endocrine neoplasia type 1 (MEN 1).

VI.2.2 Summary of treatment benefits

All the conditions for which the product is indicated require inhibition of acid secretion in the stomach.

Pantoprazole is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in the stomach. It is used for treating acid-related diseases of the stomach and intestine (reflux oesophagitis, stomach and duodenal ulcers and Zollinger-Ellison syndrome).

- Gastric reflux oesophagitis is an inflammation of the oesophagus (the tube which connects the throat to the stomach) accompanied by the regurgitation of stomach acid.
- Zollinger-Ellison syndrome is a condition caused by a gastrin-secreting tumour of the pancreas that stimulates the acid-secreting cells of the stomach.

- Peptic ulceration is a common condition consisting of a distinct break in the gastro-intestinal mucosa, usually of the stomach or duodenum, which follows abnormal exposure to the refluxed gastric contents.

The recommended daily dose of pantoprazole has demonstrated to be effective in inhibiting acid secretion in healthy volunteers and patients with gastric reflux oesophagitis. Intravenous pantoprazole 80 mg followed by additional doses of pantroprazole per hour for 24 hours maintained acid levels in the stomach above 4 during the 99% of the period studied and above 6 during the 84% of the time in 8 patients[vi]. This same pantoprazole regimen during 72 hours increased median pH to 6.3 in 14 patients with bleeding stomach or intestinal ulcers in other studies[vii,viii].

The control of elevated acid secretion was investigated in a study in 35 patients (26 of whom had Zollinger-Ellison syndrome) and in another 4 studies in patients with Zollinger-Ellison syndrome who received oral[ix,x] (18 patients) or intravenous[xi,xii] (35 patients). The wanted acid output levels were achieved and maintained in most patients. Acid output was effectively controlled for up to 6 months in 94% of patients receiving oral pantoprazole 80–240 mg/day and initial acid output was reduced in patients receiving oral pantoprazole 40–160 mg/day[xiii,xiv].

VI.2.3 Unknowns relating to treatment benefits

The benefit of treatment with pantoprazole in children is subject to some uncertainty as clinical experience in children is limited. For this reason, pantoprazole is not recommended for use in children below the age of 18 years. There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Therefore, pantoprazole should not be used during pregnancy unless clearly necessary.

Regarding breastfeeding, animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has also been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Anaphylactic reaction and anaphylactic shock	Anaphylactic reactions and anaphylactic shock was reported as rare (≥1/10,000 to <1/1.000) adverse reactions from post-marketing data.	Not preventable. Hypersensitivity to the active substance or to any of the excipients is included as a contraindication in the reference safety document. This is a standard warning, present for the majority of medicines. Pantoprazole 40 mg powder for solution for injection should be administered by a healthcare professional and under appropriate medical supervision.

Risk	What is known	Preventability
Hypomagnesaemia	Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked.	Preventable. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Hepatobiliary disorders	In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued.	Preventable. A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment.
Fracture of the hip, wrist or spine	Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors.	Preventable. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
Effect of pantoprazole on the absorption of HIV medications (atazanavir)	Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines.	Preventable. Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atanazavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.
Effect of pantoprazole on the absorption of other medicinal products (coumarin anticoagulants)	Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period.	Preventable. In patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.
Injection site thrombosis*	Injection site reactions: Thrombophlebitis was associated with the administration of intravenous pantoprazole.	Not preventable. Pantoprazole 40 mg powder for solution for injection should be administered by a healthcare professional and under appropriate

Risk	What is known	Preventability
	* Injection site thrombosis is not considered a risk for both Pantoprazol MEDE 20 mg comprimidos gastrorresistentes EFG and Pantoprazol MEDE 40 mg comprimidos gastrorresistentes EFG	medical supervision.
Gastrointestinal bacterial infection	Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.	Not preventable. Pantoprazole 40 mg powder for solution for injection should be administered by a healthcare professional and under appropriate medical supervision.

Important potential risks

Risk	What is known
Increased risk of pneumonia	Published studies have suggested a possible association between treatment with Proton Pump Inhibitors and increased risk of pneumonia.
In utero exposure and childhood asthma	A possible increased risk of childhood asthma following in utero exposure to gastric acid suppressive medication has also been reported in some studies.

Missing information

Risk	What is known
Paediatric patients	The experience in children is limited. Therefore, Pantoprazole 40 mg powder for solution for injection is not recommended for use in patients below 18 years of age until further data become available.
Use during pregnancy and breastfeeding	There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary. Regarding breastfeeding, animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has also been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Pantoprazole 40 mg powder for solution for injection has no additional risk minimisation measures. Routine pharmacovigilance should be sufficient for post-marketing safety monitoring of the risks.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

SUMMARY OF CHANGES TO THE RMP		
DATE	**VERSION NUMBER**	**CHANGES**
February 2015	01	As per RMS preliminary assessment report, the following changes to the RMP have been addressed: 1. The safety concern *Agranulocytosis was* removed. 2. The safety concern *Hypersensitivity* was removed. 3. *Anaphylactic reaction and anaphylactic shock* have been unified in one safety concern. 4. The safety concern *Hyperlipidaemia was* removed. 5. *Hepatocellular injury* and *hepatocellular failure* were unified in the safety concern *Hepatobiliary disorders*. 6. The safety concerns *Stevens-Johnson syndrome, Toxic epidermal necrolisis, and Angioedema* have been removed. 7. The safety concern *Drug interaction* was removed and two safety concerns were added: *Interaction with atazanavir* and *Interaction with phenprocoumon or warfarin*. 8. The safety concern *Interstitial nephritis* was removed. 9. *Gastrointestinal bacterial infection* has been changed from potential to important identified risk. 10. The important potential risks *Increased risk of pneumonia* and *In utero exposure and childhood asthma* were added. 11. Missing information regarding pregnant women was broaden to include use in women who are breastfeeding. 12. References to wording from Section 2.5.5 Overview of Safety from the Common Technical Document was removed from the summary of risk minimisation measures tables. 13. Section VI.2.1, VI.2.2, and VI.2.3 of the elements for a public summary were reviewed and changed in order to comply with EMA's guidance on the RMP. The summary of safety concerns (VI.2.4) was revised to reflect the updated list of safety concerns in the RMP.

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