VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Reflux esophagitis

Reflux esophagitis is a digestive disease. The reflux of stomach contents into the oesophagus (tube leading to the stomach) is known as reflux esophagitis. The most common symptom of reflux esophagitis is burning sensation in the chest. In the Western world, oesophageal reflux is a common condition. However, occurrence of oesophageal damage is two to three times more often in males both in the West and in China. In the U.S., burning sensation in the chest occurring at least once per month is reported in 36% of patients. This seems similar to the 40% occurrence of indigestion in the British population, and heartburn occurrence of 38% in Danish males and 30% in Danish females. The occurrence of esophagitis in the U.S. is approximately 7%. In non-western countries, the prevalence of esophagitis seems to be lower. It is seen during endoscopic observation in 1.5% to 5% of cases in China, 2.7% in Korea, and 2% in Germany **[Zarling EJ, 1998].**

Gastric and duodenal ulcer

An inflammatory lesion in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as a duodenal ulcer. The annual incidence of gastric ulcers varies from approximately 1 case per 1000 population in Japan to 1.5 cases per 1000 population in Norway to 2.7 cases per 1000 population in Scotland. In most countries, duodenal ulcers are about three times more common than gastric ulcers, but gastric ulcers are more common in some locations such as Japan, Sri Lanka, the Andes and some islands off northern Norway [**Pahwa R et al, 2010]**.

Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions

Zollinger-Ellison syndrome is a condition in which there is increased production of the hormone gastrin. Most of the time, a small tumour (gastrinoma) in the digestive track produces the extra gastrin in the blood. The most common initial symptom is abdominal pain and 90-95% of patients develop inflammatory lesion in the upper digestive tract. Occurrence rate ranged from 0.1% to 1% of patients in the United States. The age range of affected persons has varied from 7 to 90 years, with the majority of patients diagnosed between the age of 30 and 50 years. The disorder is found more often in men than women [**Valle JD et al, 2009]**.

VI.2.2 Summary of treatment benefits

Pivotal clinical studies were not conducted for evaluating effective and safe use of Pantoprazole Amneal 40 mg powder for solution for injection considering this is a generic medicine (generic medicine means a medicine that is developed to be the same as a reference medicine that has already been authorized). The available medical literature is considered sufficient to evaluate the safety of pantoprazole in the proposed therapeutic indication(s) for Pantoprazole Amneal 40 mg powder for solution for injection.

VI.2.3 Unknowns relating to treatment benefits

The experience of using pantoprazole in children is limited. There are no adequate data from the use of pantoprazole in pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Low level of magnesium in the blood (Hypomagnesaemia)	Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. Patient may or may not have symptoms of low magnesium. Symptoms of hypomagnesaemia are weakness, sudden involuntary muscular movement, excitement, physical disturbance, vertigo and abnormal heart beat.	Yes, for patients who are expected to take long term treatment with pantoprazole or who take proton pump inhibitors type of medicines like pantoprazole with digoxin (a medicine used for heart disease) or medicines that may cause hypomagnesaemia (like diuretics type of medicines), health care professionals should consider measuring magnesium levels before starting pantoprazole treatment and periodically during treatment. If patient gets any of symptoms of hypomagnesaemia, he or she should tell the treating physician promptly. The treating physician may decide to perform regular blood tests to monitor patient's levels of magnesium.
Bone fractures	Patients who take a proton pump inhibitor like pantoprazole, especially over a period of more than one year are at increased risk of fracture in the hip, wrist or spine. Studies suggest that proton pump inhibitors like pantoprazole may increase the overall risk of fracture by 10–40%.	Yes, patients should tell the treating physician if their osteoporosis (a condition in which bones become brittle and fragile) or if they are taking hormones related medicines like corticosteroids. Patients at risk of osteoporosis (a condition in which bones become brittle and fragile)

Risk	What is known	Preventability
		should receive care as per standard treatment guidelines and they should have an adequate intake of vitamin D and calcium.
Infection related digestive system (Gastrointestinal infections)	Proton pump inhibitors like pantoprazole might be expected to increase the counts of bacteria normally present in the upper digestive track. Treatment with pantoprazole may lead to a slightly increased risk of digestive infections caused by bacteria.	Yes, the treating physician should inform the patient regarding this side effect.
Use in patients with severe liver problem (Use in patients with severe liver impairment)	Pantoprazole is processed (metabolised) in the body via liver. Pantoprazole level is increased in patients with severe liver problems. Therefore, the liver enzymes should be monitored during therapy.	Yes, patient should tell the treating physician if patient ever had problems with liver in the past. The treating physician should check liver enzymes more frequently during treatment. In the case of a rise of liver enzymes the treatment should be stopped. A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment.
Interstitial nephritis (a kidney disorder in which the spaces between the kidney tubules become swollen)	A few cases of interstitial nephritis (a kidney disorder in which the spaces between the kidney tubules become swollen) reported during administration of pantoprazole.	Yes, the treating physician should inform the patient regarding this side effect.

Important potential risks:

Risk	What is known
Interaction with methotrexate (a class of drug which use for the treatment of inflammation in the joints and cancer) and coumarin anticoagulants (a class of drug which prevents or retards the clotting of blood)	Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered. A few cases reported changes in International Normalised Ratio (a laboratory test for blood clotting) during administration of pantoprazole together with coumarin anticoagulants in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants, monitoring of prothrombin time (a laboratory test for blood clotting) / International Normalised Ratio is recommended after initiation, termination or during use of pantoprazole.

Missing information:

Risk	What is known
Use in pregnancy and lactation	Studies in animals have shown reproductive side effects following use of pantoprazole. There are no adequate data from the use of pantoprazole in pregnant women. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy, unless clearly necessary. Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has 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 additional risk minimization measures by safety concern

Summary of Product Characteristics (SPC) of Pantoprazole Amneal 40 mg powder for solution for injection 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 (PIL). All these risk minimization measures are given in SPC and PIL of Pantoprazole Amneal 40 mg powder for solution for injection.

No additional risk minimization measures have been proposed for this generic medicine.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

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

Version	**Date (dd-mm-yyyy)**	**Safety Concerns**	**Comment**
01	16-04-2015	Important identified risks • Hypersensitivity to pantoprazole or to any of the excipients • Hypomagnesaemia • Bone fractures • Gastrointestinal infections • Use in patients with severe liver impairment Important potential risks • Use in pregnancy • Use in breast feeding • Concomitant administration with atazanavir • Concomitant administration with coumarin anticoagulants Missing information • Use in paediatric patients	Nil
02		Important identified risks • Hypomagnesaemia • Bone fractures • Gastrointestinal infections • Use in patients with severe liver impairment • Interstitial nephritis Important potential risks • Interaction with methotrexate and coumarin anticoagulants Missing information • Use in pregnancy and lactation	Revised as per agency suggestion