### VI.2.1 Overview of disease epidemiology

**Reflux oesophagitis (reflux of stomach contents into the oesophagus):**

In the Western world, esophageal reflux is a common condition. Reflux can present at any age, but seems most common in the 20 to 50 year age group. Symptoms occur equally often in males and females, and the likelihood of hospitalization is similar for the two genders. This seems similar to the 40% prevalence of dyspepsia (indigestion) in the British population, and heartburn prevalence of 38% in Danish males and 30% in Danish females. The prevalence of esophagitis in

the U.S. is approximately 7%. As individual patients age, they become less likely to experience symptoms of reflux but their risk for esophageal damage remains constant. Mild and moderate obesity is strongly associated with the development of reflux.

**Gastric and duodenal ulcer (distinct breach in the mucosa of the stomach as a result of caustic effects of acid):**

The incidence of stomach ulcer peaked in the 1950s– 1960s and has been in decline for the last few decades. Despite this decline, stomach ulcer remains a common and important disease. According to the National Health Service, approximately 1 in 8 people in the UK will develop a stomach ulcer at some time in their lives. Persons with a history of stomach ulcer have a fivefold increased risk of complications of upper part of the digestive system. Common known risk factors for stomach ulcer include infection with a type of bacteria (Helicobacter pylori) (H. pylori), smoking, heavy alcohol drinking and use of pain killers.

**Zollinger-Ellison-Syndrome (ZES) and other pathological hypersecretory conditions (increased production of the hormone gastrin that stimulates the acid-secreting cells of the stomach):**

The ZES, is characterized by stomach ulcers of the upper part of the digestive system resistant to medical therapy, diarrhea and severe stomach acid over secretion associated with tumors of certain type of pancreas cells. It was later demonstrated that this pancreatic tumor, named gastrinoma (tumor in the pancreas or duodenum), abnormally releases gastrin (a type of hormone), which is responsible for the stomach acid over secretion. Most gastrinomas arise from the duodenum (first part of the small intestine), whereas they are localized in the pancreas in 25% of cases. This tumor presents itself at various ages from 7 to 90 years, but the diagnosis is usually made between the ages of 30 and 50 years. Its frequency of occurrence is reported to be approximately the same as insulinoma (tumor of the pancreas). Incidence is 1-3 cases per million patients per year in Sweden, 0.5 cases per million patients per year in Ireland, and 0.1-0.2 cases per million patients per year in Denmark.

### VI.2.2 Summary of treatment benefits

Accord pantoprazole 40 mg powder for solution for injection is used for treating:

- Reflux oesophagitis (an inflammation of oesophagus (the tube which connects throat to stomach) accompanied by the regurgitation (expulsion) of stomach acid):

A multicenter, study of the therapeutic effects of pantoprazole (Intravenous) for Injection and oral pantoprazole. Patients with reflux of stomach contents into the oesophagus (Gastroesophageal reflux disease) and a history of inflammation of the esophagus (erosive esophagitis) were given either 40 mg intravenous pantoprazole, 40 mg oral pantoprazole, or dummy drug once daily for 7 days. This study demonstrated that, after treatment for 7 days, patients treated with pantoprazole Intravenous. for Injection had a significantly lower Maximum acid output (MAO) and normal acid output than those treated with placebo, and results were comparable to those of patients treated with oral pantoprazole.

- Stomach and duodenal ulcer:

Study evaluating patients with healed ulcer of upper part of intestine after 2 weeks of treatment and patients unhealed at 2 and after 4 weeks of treatment. Men or women, aged at least 18 years, with one or two duodenal ulcers. Pantoprazole 40 mg daily and omeprazole 20 mg daily are equally effective in inducing ulcer healing.

- Zollinger-Ellison-Syndrome and other conditions producing too much acid in the stomach:

An initial treatment with pantoprazole I.V. for Injection in 21 patients reduced acid output to the target level and significantly reduced hydrogen ion concentration (pH: measure of the) and the volume of stomach secretions; target levels were achieved within 45 minutes of drug administration.

Accord has not conducted any studies for pantoprazole on expected benefit considering its similarity to the currently marketed product (Protium IV, Takeda UK Ltd).

### VI.2.3 Unknowns relating to treatment benefits

Not known

### VI.2.4 Summary of safety concerns

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Hypersensitivity (having the immune system react too much to a medicine or drug) | Accord Pantoprazole is Contraindicated to patients having hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients.<br>Rarely Hypersensitivity (including anaphylactic reactions and anaphylactic shock) are known to occur with pantoprazole. | Yes<br>Patient must not be given Pantoprazole if patient is allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole Sodium Injection or to medicines containing other proton pump inhibitors. |
| Severe damage to liver/<br>liver cells (Hepatocellular injury and hepatic failure) | Pantoprazole may uncommonly result in increase in liver enzymes (transaminases, γ-GT) and rarely increase bilirubin level. | Yes<br>One should tell doctor if is having any severe liver problems or ever had problems with liver in the past. Doctor will check liver enzymes more frequently. In the case of a rise of liver enzymes the treatment should be stopped. |

| Risk | What is known | Preventability |
|---|---|---|
| Bacterial gastrointestinal infections | Pantoprazole Sodium Injection has been associated with a small increase in infectious diarrhoea.<br>PPIs may increase the counts of bacteria normally present in upper part of the digestive system. When used pantoprazole there is slightly increased risk of digestive system infections caused by bacteria such as *Salmonella* and *Campylobacter* | Yes<br>Doctor should be contacted if symptoms of digestive system infections are noticed. |
| Low blood levels of magnesium (Hypomagnesaemia) | If receiving pantoprazole for more than three months it is possible that the levels of magnesium in blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. | Yes<br>If one gets symptoms of fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate, please tell your doctor promptly. Doctor may decide to perform regular blood tests to monitor levels of magnesium. |
| Bone Fractures | Taking a proton pump inhibitor like pantoprazole, especially over a period of more than one year, may slightly increase your risk of fracture in the hip, wrist or spine. | Yes<br>Tell your doctor if you have brittle bones (osteoporosis) or if you are taking corticosteroids (which can increase the risk of |

| Risk | What is known | Preventability |
|---|---|---|
| | | osteoporosis). |
| Interaction with atazanavir | When taken a medicine containing atazanavir (for the treatment of HIV-infection) whose absorption is pH dependent, with proton-pump inhibitors it might result in a substantial reduction in the extent to which these HIV medications become available to the body of and might impact the efficacy of these medicines. | Yes<br>Tell your doctor or pharmacist, if you are using other medicines, have recently used other medicines, or intend to use other medicines. This includes medicines that you buy without a prescription. This is because pantoprazole can affect the way some medicines work and some medicines can have an effect on pantoprazole. |
| Interaction with Phenoprocoumon or warfarin | As per data available from post marketing period few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment of pantoprazole and coumarin anticoagulants warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. | Yes<br>Tell your doctor or pharmacist, if you are using other medicines, have recently used other medicines, or intend to use other medicines. This includes medicines that you buy without a prescription. This is because pantoprazole can affect the way some medicines work and some medicines can have an effect on pantoprazole.<br>In patients treated with coumarin |

| Risk | What is known | Preventability |
|---|---|---|
| | | anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole. |
| Chronic treatment with PPIs (Proton Pump Inhibiotors) decreases absorption of Vitamin B12 (cyanocobalamine) | None | None |
| Visual disturbances | Rare side effects of Pantoprazole include disturbances in vision such as blurred vision | If you get this side effect, please tell your doctor promptly. |

**Important potential risks**

| Risk | What is known |
|---|---|
| Lung infection (Pneumonia) | Stomach acid is an important barrier against pathogen invasion through the digestive system. Potential pathophysiological mechanisms for the association of pneumonia with PPI use include possible increased bacterial growth and colonisation of the upper part of digestive system with subsequent translocation to the respiratory tract. Similarly, PPIs may cause |

| Risk | What is known |
|---|---|
| | alterations in the pH value of the respiratory tract which may allow growth of respiratory pathogens. PPIs have also been found to negatively affect the immune system. |
| Use in pregnancy and risk of childhood asthma | None |
| Congenital cardiac malformation following in utero exposure | None |
| Decrease in absorption of iron | None |
| Interactions with Phenytoin | None |
| Interactions with Nelfinavir | None |
| Interactions with Digoxin | For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause low levels of magnesium in blood (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. |
| Interactions with Methotrexate | 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 |

| Risk | What is known |
|---|---|
| | need to be considered. |
| Interactions with Tacrolimus | None |
| Interactions with Clopidogrel | None |

**Missing information**

| Risk | What is known |
|---|---|
| Limited information on the use in pediatric population | The experience in children is limited. Therefore, Pantoprazole 40 mg is not recommended for use in patients below 18 years of age until further data become available.<br>These injections are not recommended for use in children under 18 years of age. |
| Limited information on the use in pregnant and lactating women | There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported. If one is pregnant, or think may be pregnant, or if are breast-feeding, one should use this medicine, only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.<br>Ask your doctor or pharmacist for advice before taking any medicine. |
| Use in patients with kidney (renal) impairment | No dose adjustment is necessary in patients with impaired renal function. |

### 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.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

### VI.2.7 Summary of changes to the risk management plan over time

| Version | Date | Safety Concern | Comment |
|---|---|---|---|
| 3.0 | 08-Aug-2014 | No changes in the safety concerns | Part VI.2.1 Overview of disease epidemiology and VI.2.2 Summary of treatment benefits have been updated as per Day 120 Assessment report (UK/H/5591/001/DC) |
| 2.0 | 22-April-2014 | Following safety concerns are added:<br>**Important identified risks:** Chronic treatment with PPIs | Part VI.2.1 Overview of disease epidemiology and VI.2.2 Summary of |

| Version | Date | Safety Concern | Comment |
|---|---|---|---|
| | | decreases absorption of Vitamin B12 (cyanocobalamine)<br>Visual disturbances<br>Hepatocellular injury and hepatic failure were merged into a single important identified risk.<br>**Important potential risk:**<br>Use in pregnancy and risk of childhood asthma<br>Congenital cardiac malformation following in utero exposure<br>Decrease in absorption of iron<br>Interactions with Phenytoin<br>Interaction with Nelfinavir<br>Interaction with Digoxin<br>Interaction with Methotrexate<br>Interaction with Tacrolimus<br>Interaction with clopidogrel<br>**Missing Information:**<br>Use in patients with renal impairment | treatment benefits have been updated. |