VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pantoprazole is used to treat diseases: Symptomatic gastro-oesophageal reflux disease, reflux oesophagitis, Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs.

Gastro-oesophageal reflux disease is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. According to this definition, "troublesome" symptoms are those that adversely affect an individual's well-being.

Gastroduodenal ulcer is a lesion of the skin or a mucous membrane such as the one lining the stomach or duodenum that is accompanied by formation of pus and necrosis of surrounding tissue, usually resulting from use non-steroidal anti-inflammatory drugs.

VI.2.2 Summary of treatment benefits

Pantoprazole is used to treat diseases where the stomach produces too much acid. These include: reflux disease to treat symptoms such as heartburn and acid regurgitation (acid flowing up in the mouth), reflux oesophagitis (inflammation of the gullet, due to acid).

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Drug interaction between PPIs and clopidogrel	Information related to drug interaction between PPIs and clopidogrel is published by Regulatory authorities like FDA but Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	Physician supervision and care.
Chronic treatment with PPIs and 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	Physician supervision and care.

Risk	What is known	Preventability
	hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.	
Increased risk of fractures of the hip, wrist, and spine with the long term use of PPIs	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. 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. Frequency of this events is *Uncommon* in patients being treated with Pantoprazole.	Physician supervision and Care.
Visual disturbances	Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.	
Microscopic colitis	This issue of Microscopic colitis is under review by Aurobindo. MAH will continue to be monitored through routine pharmacovigilance and an updated RMP will be submitted with the result of new information being received that may lead to a significant change to the risk of microscopic colitis.	Physician supervision and Care.

Risk	What is known	Preventability

Important potential risks

Risk	What is known	Preventability
Increased risk of Clostridium difficile–associated diarrhoea (CDAD) with PPIs	Information related to drug Increased risk of Clostridium difficile–associated diarrhoea (CDAD) with PPIs is published by Regulatory authorities like FDA but Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	Physician supervision and care.
Chronic use of PPIs and the risk of pneumonia	Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	Physician supervision and care.
Congenital cardiac malformation following in utero exposure	Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	
Decrease in absorption of iron	Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	
Off-label use	Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	
Interactions with Warfarin or other coumarine derivatives, Phenytoin, Atazanavir, Nelfinavir, Digoxin, Methotrexate, Tacrolimus, Clopidogrel	*Co-administration with atazanavir* Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical	

Risk	What is known	Preventability
	monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded. *Coumarin anticoagulants (phenprocoumon or warfarin)* 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. Therefore, 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. *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. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended. Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with	

Risk	What is known	Preventability
	p-glycoprotein related absorption of digoxin. Interactions with Phenytoin, Atazanavir, Nelfinavir, Methotrexate, Tacrolimus, Clopidogrel: Periodic comparison of safety-related sections of the Aurobindo SPC will be done to update Aurobindo SPC in line with the SPC of the innovator/reference product.	

Missing information

Risk	What is known	Preventability
Use in pregnancy and during lactation	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 Aurobindo should not be used during pregnancy unless clearly necessary.	Physician supervision and care.
Use in patients with renal impairment	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 Aurobindo should be made taking into account the benefit of breast- feeding to the child and the benefit of Pantoprazole Aurobindo therapy to women.	Physician supervision and care.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

Safety concern in lay terms (medical term)

Risk minimisation measure(s)
Objective and rationale
• Summary description of main additional risk minimisation measures – key points

Risk minimisation measure(s)
None

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

None.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 2.0	07 June 2013	V1.0 is amended with new important identified risks, Important Potential risks & Important missing information are included in the current RMP.	RMP is updated by including the new safety concerns.
Version 3.0	18 December 2013	V2.0 is amended with addition of new safety concern “Microscopic colitis” under Important identified risk section as suggested by assessor	RMP is updated in accordance with new EU format.