VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Rabeprazole (ATC code A02B C04) is a proton pump inhibitor (PPI) that regulates the acid gastric. The main representative of this class is Omeprazole, the first PPI used in clinical praxis for the treatment of alterations in the gastric acid secretion. Nowadays, a profuse experience on drug effectiveness and safety is available.
PPIs have been successful both clinically and commercially for the treatment of various acid-related disorders; mainly gastroesophageal reflux disease (GERD). Other indicated uses of PPIs include the treatment and prevention of upper gastrointestinal (GI) tract ulcers from nonsteroidal antiinflammatory drugs (NSAIDs), as part of therapeutic regimens for eradication of Helicobacter pylori infection, and in the management of patients with bleeding peptic ulcer.

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage, mainly in the stomach and proximal duodenum and less commonly in the lower esophagus, the distal duodenum, or the jejunum.
The incidence of the disease in the occidental world is high (6-15% of the population will suffer it
in their lives). The prevalence of duodenal ulcer ranges between 1.4-1.8%, and incidence between 0.06 and 0.29%.
It usually appears in the forties, lying the highest rate between 55 and 65 years old. A genetic predisposition to peptic disease may exist since it is more frequent in patients whose relatives have suffered from it.
Peptic ulcer ethio-pathogenesis seems to be multi-factorial. There is an imbalance between the defense mechanisms of the gastro-duodenal barrier and the aggression mechanisms.
(Ramakrishnan and Salinas, 2007).
In addition, it is necessary to take into account that peptic ulcer disease is a chronic disease with a high risk of relapse once treatment is withdrawn; if left untreated the relapse rate of duodenal ulcer is 50-80% per year.

NSAIDs use is very common in clinical practice. The incidence of NSAIDs-associated gastric and duodenal ulcers and bleedings differs according to authors, but NSAIDs use could be the predominant cause in 24% of cases.

GERD is defined as a "condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications." Heartburn, estimated to occur daily in 7% of the U.S. population, is the most common symptom of GERD. Between 20% and 40% of those experiencing common heartburn are predicted to actually have a diagnosis of GERD.

In 1995, Zollinger and Ellison described a frequently fulminating syndrome characterised by multiple peptic ulceration, marked hypersecretion pancreatic tumours (Zollinger and Ellison, 1955). Except for the symptoms due to gastrinoma metastasis (at least a 60% of the gastrinomas are malignant), the main clinical manifestation of Zollinger-Ellison syndrome is due to high plasma levels of gastrin. It is difficult to accurately predict the prevalence and the incidence of Zollinger-Ellison syndrome, because the use of PPIs can mask the symptoms of acid hypersecretion, preventing the diagnosis of this syndrome.

Numerous studies in various countries showed that the stomach of more than 50% of world adult population contains H. pylori, which is able to induce gastritis in all infected subjects and peptic ulcers in about 10-15% of them. It means that the incidence of the peptic ulcer has to be between 5 and 10% of Word population.

VI.2.2 Summary of treatment benefits

A series of clinical trials has been performed in order to evaluate the clinical efficacy of rabeprazole. All these studies proved this product to be highly effective in the treatment of Symptomatic erosive or ulcerative gastroesophageal reflux disease (GERD), Gastroesophageal reflux disease, long-term management (GERD maintenance therapy), Symptomatic treatment of moderate to very severe GERD, Duodenal ulcer and benign gastric ulcer, Eradication of Helicobacter pylori in patients with peptic ulcer disease in combination with appropriate antibiotic regime and Zollinger-Ellison Syndrome.

VI.2.3 Unknowns relating to treatment benefits

No other evidence of efficacy has been detected.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Drug interaction between PPIs and clopidrogel	An interaction is observed between clopidogrel and rabeprazole. The clinical relevance of this interaction is uncertain.	As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Chronic treatment with PPIs and hypomagnesaemia	Severe hypomagnesaemia has been reported in patients treated with PPIs like Rabeprazole sodium for at least three months, and in most cases for a year.	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

Risk	What is known	Preventability
		treatment.
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.	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.
Chronic treatment with PPIs decreases absorption of cyanocobalamine (vitamin B12)	Rabeprazole may reduce the absorption of vitamin B12 (cyanocobalamin).	Health care professionals should consider this in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
Visual disturbances	Adverse drug reactions such as dizziness and visual disturbances may occur in patients under therapy with rabeprazole.	Patient should inform the doctor in case of visual disturbances.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Increased risk of Clostridium difficile-associated diarrhoea (CDAD) with PPIs	Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile. Decreased gastric acidity due to any means, including proton pump inhibitors such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract.
Chronic use of PPIs and the risk of pneumonia	Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
Congenital cardiac malformation following in utero exposure	There are no data on the safety of rabeprazole in human pregnancy. Rabeprazole is contraindicated during pregnancy.
Decrease in absorption of iron	Rabeprazole sodium produces inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary. Absorption of iron could be reduced when administered with some drugs and food
Off-label use	Rabeprazole is not recommended for use in children, as there is no experience of its use in this group.
Interactions with: warfarin or other coumarine derivates, Phenytoin, Atazanavir, Nelfinavir, Digoxin, Methotrexate, Tacrolimus	Rabeprazole may interact with these products. Patient should inform the doctor before staring therapy with rabeprazole.

Missing information

Risk	What is known
Use in pregnancy and during lactation	*Pregnancy* There are no data on the safety of rabeprazole in human pregnancy. Rabeprazole is contraindicated during pregnancy. *Lactation* It is not known whether rabeprazole sodium is excreted in human breast milk. Therefore rabeprazole should not be used during breast feeding.
Use in patients with renal impairment	No dosage adjustment is necessary for patients with renal or hepatic impairment.

VI.2.5 Summary of risk minimization measures by safety concern

Summary of Product Characteristics (SmPC) of rabeprazole 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). All these risk minimization measures are given in SmPC and PL of rabeprazole.

This medicine has no additional risk minimization measures.

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

This section is not applicable as this is version 01 of RMP.