EU RISK MANAGEMENT PLAN (EU – RMP)

Active substance(s) (INN or common name):	Esomeprazole
Pharmaco-therapeutic group (ATC Code):	A02B C05
Name of Marketing Authorisation Holder or Applicant:	Sigillata Limited
Strength and pharmaceutical form:	20mg and 40mg gastro resistant tablets

Data lock point for this RMP	November 2013	Version number	1.1
Date of final sign off	30/12/2013		

Elements for a public summary

VI.2.1 Overview of disease epidemiology

Esomeprazole is a medicine which is used in adults for the treatment of reflux symptoms (sometimes called acid reflux), such as heartburn and acid regurgitation. It is also used to heal or prevent peptic ulcers in certain types of patients. This medicine works by reducing the amount of acid that the stomach produces.

Gastroesophageal reflux disease

Partly as a result of diet and lifestyle, some adults living in the Western world have become prone to acid reflux (acid leaking from the stomach upwards into the oesophagus or gullet). It is as common in women as in men, but more likely in people over the age of 40. Unlike the stomach, the gullet is not meant to have acid in it and so this acid leakage can damage the lining of the gullet and can cause symptoms like heartburn and may even cause the gullet to develop an ulcer.

Zollinger-Ellison syndrome

The disease called Zollinger-Ellison syndrome is caused by a particular type of tumour in the pancreas. This type of tumour causes the cells which produce the acid in the stomach to work more than usual and produce too much acid. As a result of this increased amount of acid, some of it can leak upwards out of the stomach into the gullet. The lining of the gullet is different from the lining of the stomach and is not protected from being damaged by the acid, meaning that it may cause symptoms like heartburn and acid reflux or acid regurgitation. Many kinds of people can be affected by this disease, but it usually occurs over the age of 40 – 50 years and is slightly more common in men.

Peptic ulcer

Stomach ulcers and duodenal ulcers (which develop in the duodenum, the next part of the bowel after the stomach) are often referred to as peptic ulcers. Peptic ulcers are quite common and about 10% (1 in 10) people will suffer from this problem at some time in their life. Peptic ulcers can affect people of any age, though they are more common over the age of 60. They can be caused by a particular type of bacteria in the stomach (called Helicobacter pylori) which irritates the lining of the stomach causing an ulcer to form; or certain kinds of drugs which can damage the stomach lining (particularly certain types of pain killers called non-steroidal anti-inflammatory drugs or NSAIDs). Drugs like esomeprazole which reduce the amount of acid in the stomach will help the ulcer to heal.

VI.2.2 Summary of treatment benefits

Esomeprazole has been tested in Clinical Trials in a total of over 15,000 people worldwide to be effective in each of the indications stated above.

Gastro-oesophageal reflux disease

Studies were conducted to test the effectiveness of esomeprazole in 6709 patients who had developed erosions (ulcers) in the gullet caused by acid reflux. Most studies compared esomeprazole with placebo (dummy treatment). The main measure of effectiveness was the healing rate of the ulcers over the first 4 and 8 weeks of the study. By the end of 8 weeks approximately 90% (9 out of 10) of patients had been healed. A further 808 patients were studied to look at long term healing of the ulcer after 6 and 12 months. Approximately 90% of patients remained healed. In 717 patients with symptoms of acid reflux, where the main measure of effectiveness was relief of symptoms of heartburn, up to 75% (three quarters) of patients were symptom free after one month.

Zollinger-Ellison syndrome

A small study showed that 18 out of 20 patients tested had their acid production controlled after one year of treatment.

Peptic ulcer

Esomeprazole in combination with 2 antibiotics was tested in two major studies in a 10 day treatment of peptic ulcer caused by Helicobacter pylori. In each study the bacteria were cleared in approximately 84% of patients after one month. In those patients, the peptic ulcer was healed at one month in 75% and 57% of patients in one or the other study. Two studies were also conducted in patients at risk of developing peptic ulcers as a result of needing to take NSAID drugs regularly. A total of 1429 patients were tested but as there was a very low incidence of ulcers in any patients it was impossible to see whether or not esomeprazole helped.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, there is no evidence to suggest that treatment results would be different in any subgroup of the studied population, taking into account factors such as age, sex, race, or organ impairment. Limited data is available regarding treatment in children and the effects of long-term treatment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Lack of white blood cells (Agranulocytosis)	Changes in the blood count including agranulocytosis (lack of white blood cells) are very rare and may affect up to 1 in 10,000 people.	Esomeprazole may in very rare cases affect the white blood cells leading to immune deficiency. A lack of white blood cells (agranulocytosis) can be ruled out by a blood test.
Allergic reactions (Hypersensitivity reactions)	In people allergic to esomeprazole or any of the ingredients, an allergic reaction may develop. Signs of an allergic reaction include sudden wheezing, swelling of the lips, tongue and throat or body, rash, fainting or difficulties in swallowing.	Esomeprazole should not be used in patients with a history of an allergic reaction to this medicine or any of its ingredients. If any signs of an allergic reaction develop, the medicine should be stopped immediately.
Low levels of magnesium in the blood (Hypomagnesaemia)	Treatment for longer than three months may cause the levels of magnesium in the blood to 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.	If any of these symptoms develop, a doctor should be informed promptly. Regular blood tests may be required to monitor the levels of magnesium.
Low mood (Depression)	Esomeprazole may cause a person to be depressed. This is rare and can affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Liver problems, including jaundice (Hepatitis)	There is a potential for patients to develop side effects relating to the liver during treatment with esomeprazole. Symptoms may include yellow skin, dark urine and tiredness.	If these symptoms occur contact the doctor.

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Liver failure (Hepatic failure)	Severe liver problems leading to liver failure may affect up to 1 in 10,000 people.	Patients with severe liver problems may require a lower dose.

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Inflammation of the brain due to liver failure (Hepatic encephalopathy)	Severe liver problems leading to liver failure and inflammation of the brain may affect up to 1 in 10,000 people.	Patients with severe liver problems may require a lower dose.

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Severe skin rash (Erythema multiforme)	Sudden onset of a severe rash or blistering or peeling skin is very rare and may affect up to 1 in 10,000 people.	Patients should be made aware of this risk.
Severe skin rash or blistering or peeling skin	Reddening of the skin with blisters or peeling may develop. There may also be severe blisters	Patients should be made aware of this risk.

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
(Stevens-Johnson syndrome/Toxic epidermal necrolysis)	and bleeding in the lips, eyes, mouth, nose and genitals. This is very rare and may affect up to 1 in 10,000 people.	

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Severe kidney problems (Interstitial nephritis)	Severe kidney problems may develop but are very rare and may affect up to 1 in 10,000 people.	Caution is advised when treating patients with severe underlying kidney problems.

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Wheezing and shortness of breath (Bronchospasm)	This is rare and may affect up to 1 in 1,000 people.	Patients should be made aware of this risk.
Fracture of the hip, wrist or spine	Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may increase the risk of hip, wrist and spine fracture, particularly in the elderly or in patients with risk factors.	Caution is advised in treating patients with osteoporosis or in patients being treated with corticosteroids.

Taken together with other medicines such as nelfinavir/atazanavir (used to treat HIV), phenytoin (used in epilepsy), medicines that are used to thin your blood, such as warfarin, digoxin (used for heart problems), methotrexate (a chemotherapy medicine used in high doses to treat cancer). tacrolimus and clopidogrel (Drug interaction)	If these medicines are taken together with esomeprazole, they may affect the way the other medicine works.	Caution is advised when taking these medicines together.

Important potential risks

Risk	What is known
Fits (convulsion/seizure)	There is a potential increased risk of fits particularly with a low level of magnesium in the blood.
Use during pregnancy and the risk of asthma in children (Use of acid-suppressing drugs in pregnancy and risk of childhood asthma)	There is a potential increased risk of asthma in children if esomeprazole is used during pregnancy.

Missing information

Risk	What is known
Long term treatment in children	Data is lacking concerning the long term use of esomeprazole in children

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

No additional risk minimisation activities are required. Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

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

There are no studies in the post authorisation development plan.

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

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1.0	20/05/2013	**Important identified risks** • Use in severe renal impairment • Use in severe hepatic impairment • Interaction with CYP3A4 inhibitors • Interaction with CYP2C19 inhibitors or inducers • Gastrointestinal perforation • Use in patients with gastric ulcers • Psychiatric disorders • Interference with laboratory tests • Hypomagnesaemia • Interaction with clopidogrel • Increased risk of fractures • Reduction of vitamin B12 absorption • Co-administration with atazanavir • Co-administration with warfarin	N/A

Version 1.1	Under review	**Important identified risks** • Agranulocytosis • Hypersensitivity reactions • Hypomagnesaemia • Depression • Bronchospasm • Hepatitis with or without jaundice • Hepatic failure • Hepatic encephalopathy • Erythema multiforme • Steven's Johnson syndrome/Toxic epidermal necrolysis • Interstitial nephritis • Fracture of the hip, wrist or spine • Drug interaction with warfarin or other coumarine derivatives, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, tacrolimus, clopidogrel **Important potential risks** • Convulsion/seizure • Use of acid-suppressing drugs in pregnancy and childhood asthma **Missing information** • Long term treatment in children	Safety concerns were updated in-line with the originator product