Excerpt from EU Risk Management Plan

Drug substance: Esomeprazole

Date 8 March 2016

VI. 2 Elements for a Public Summary. Excerpt from esomeprazole EU Risk Management Plan, version 12, 8 March 2016

TABLE OF CONTENTS PAGE

1. EXCERPT FROM ESOMEPRAZOLE EU RMP

VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

VI: 2.1 Overview of disease epidemiology

VI: 2.1.1 Gastroesophageal reflux disease

Disease description

This disease is also called 'GERD', which is the short form for GastroEsophageal Reflux Disease. In reflux disease, the backflow of stomach contents into the food pipe (esophagus), throat and possibly into the mouth leads to troublesome reflux symptoms (eg, heartburn) in some individuals. In some of these individuals, this backflow leads to inflammation in the lower part of the food pipe called 'reflux esophagitis'.

Prevalence and disease occurrence

Each year, approximately 0.5% of adults and 0.1–1% of children are diagnosed with GERD. In total, about 10–20% of adults and 1–8% of children are reported to have GERD. Approximately 40% of individuals with GERD have reflux esophagitis.

Risk factors

GERD becomes increasingly common with age. GERD is more common in the elderly than in younger people. Men and women are equally likely to have GERD.

The likelihood of developing GERD is increased in people with:

- hiatus hernia, a condition in which the upper part of the stomach protrudes upwards through the muscle (diaphragm) that separates the belly from the chest
- an abnormal lower oesophageal sphincter, which is the ring of muscles at the lower end of the oesophagus (where it meets the stomach) that stops stomach contents coming back up into the oesophagus
- disorders that slow down the emptying of stomach contents into the small intestine
- obesity (compared with healthy weight), especially if the excess body fat is distributed around the stomach and abdomen
- previous occurrence of ulcers in their stomach (gastric ulcer) or the first part of their small intestine (duodenal ulcer) in the past; an ulcer is a break in lining of the stomach or intestine that looks like a sore.

Pregnant women are more likely to develop GERD. In children, neurological (brain or nerve) disabilities or esophageal diseases that are present at birth are associated with an increased risk of GERD. GERD in childhood may increase the risk of GERD in adulthood.

Main treatment options

Acid-suppression is the main treatment for GERD. Proton pump inhibitors (PPIs), such as esomeprazole, block acid production in the stomach, and are highly effective at preventing GERD symptoms and healing reflux esophagitis. Histamine-receptor blockers, such as ranitidine, partially block acid production in the stomach and can be used to treat GERD symptoms and heal esophagitis. Antacids (substances that neutralize stomach acid) may be effective in alleviating feeling of heartburn or indigestion. Prokinetic agents, such as metoclopramide and domperidone, increase movement in the gut; they may be used in addition to a PPI in patients with only a partial symptomatic response to PPI therapy, but they are limited by their possible side effects. Recent data indicate that weight loss may have a beneficial effect on occurrence and severity of heartburn and regurgitation. Anti-reflux surgery or endoscopic therapy may be considered in some patients.

Mortality and morbidity

GERD does not affect long-term survival. Reflux esophagitis is the most common complication of GERD. Less common complications of GERD are esophageal stricture (an abnormal narrowing), bleeding and, rarely, Barrett's esophagus (condition in which the cells of lower esophagus become damaged) and cancer of the esophagus.

VI: 2.1.2 Reflux symptoms (eg, heartburn and acid regurgitation)

Disease description

Heartburn and acid regurgitation are characteristic symptoms of reflux disease, though these symptoms can be associated with other diseases as well. The most characteristic reflux symptoms are 'burning feeling behind your breastbone (heartburn)' and 'stomach contents moving upwards to your throat and mouth (regurgitation)'. Most individuals experience such symptoms at times, but in patients with reflux disease they are troublesome and difficult to cope with. See section VI: 2.1.1 Gastroesophageal reflux disease/Disease description.

Prevalence and disease occurrence

Each year, approximately 0.1% of adults are diagnosed with heartburn. In total, about 10 20 % of adults experience heartburn at least once per week.

Risk factors

Heartburn becomes increasingly common with age. Women are more likely than men to develop heartburn as are people with obesity and pregnant women. See section VI: 2.1.1 Gastroesophageal reflux disease/Risk factors.

Main treatment options

The main treatment options to relieve reflux symptoms are acid-suppressive agents and antacids. See section VI: 2.1.1 Main treatment options. Antacids and over-the-counter acid-suppressants are options for patient-directed therapy for heartburn and regurgitation. When symptoms persist, continuous therapy is required or specific symptoms or signs develop such as difficulty swallowing, painful swallowing, weight loss and chest pain, the patient should have additional evaluation and treatment.

Mortality and morbidity

See section VI: 2.1.1 Mortality and morbidity.

VI: 2.1.3 Peptic ulcer disease

A peptic ulcer (an ulcer of the stomach (gastric ulcer) or duodenum (duodenal ulcer), also known as peptic ulcer disease is a common condition. The most common cause is an infection with *Helicobacter pylori*. Peptic ulcers can also be caused or worsened by drugs such as NSAIDs.

Helicobacter pylori associated duodenal ulcer

Disease description

Helicobacter pylori (H. pylori) is a bacterium that can live in the stomach. Infection with *H. pylori* is one of the most important causes of peptic ulcer. A peptic ulcer may go deep into the stomach or duodenal wall and then cause damage to blood vessels, leading to bleeding into the stomach or intestine. Another possible complication of peptic ulcer is a perforation (puncture) of the stomach lining or duodenum, causing stomach or intestinal contents to leak into the abdomen.

Prevalence and disease occurrence

Each year, approximately 0.04–0.06% of adults are diagnosed with uncomplicated duodenal ulcers. In total, about 2–4% of adults have duodenal ulcers. About 60% of individuals with duodenal ulcers are infected with *H. pylori*.

Risk factors

The main routes for *H. pylori* infection are contact from person to person and drinking contaminated water. The main risk factors for *H. pylori*-associated duodenal ulcer are the *H. pylori* infection itself (especially certain type of *H. pylori* that produces toxic factors) and in addition old age, history of a previous duodenal or stomach ulcer.

Main treatment options

The main treatment for *H. pylori* infection is a 7-10 days course of a PPI given together with two antibiotics. After initial treatment, continued PPI therapy is recommended for patients with complicated duodenal ulcers.

Mortality and morbidity

In patients with uncomplicated ulcer disease, the death rate in the year after diagnosis is about four times higher than that in the general population. The death rate is higher in patients with ulcer complications, including bleeding or perforation.

Nonsteroidal anti-inflammatory drug-associated peptic ulcer

Disease description

NSAIDs (nonsteroidal anti-inflammatory drugs) are generally prescribed for the long-term treatment of arthritic pain and inflammation. ASA (aspirin), which is also an NSAID, is most commonly prescribed to protect the heart. Use of NSAIDs, including ASA, increases the risk of developing peptic ulcer disease. When *H. pylori* infection is present the risk further increases.

Prevalence and disease occurrence

Each year, approximately 0.08–0.1% of adults are diagnosed with peptic ulcers. In total, about 4–6% of adults have peptic ulcers. Peptic ulcer disease is potentially related to use of NSAIDs (including ASA) in about 40–50% of cases.

Risk factors

The main risk factors for duodenal and gastric ulcers associated with use of NSAIDs including acetylsalicylic acid (aspirin, ASA) are old age, multiple uses of NSAIDs, *H. pylori* infection and the history of peptic ulcer disease.

Main treatment options

Acid-suppressive therapy such as histamine-receptor blockers or PPI therapy is recommended in patients with NSAID-associated peptic ulcer disease who need to continue taking NSAIDs. Testing for *H. pylori* infection should be considered in patients requiring long-term NSAID therapy; if positive, patients should receive treatment.

Mortality and morbidity

See section VI: 2.1.3 Peptic ulcer disease/Helicobacter pylori associated duodenal ulcer/Mortality and morbidity.

Peptic ulcer bleeding and rebleeding

Disease description

A bleeding peptic ulcer is a medical emergency. Initial treatment is to stop the bleeding through endoscopic therapy (an endoscope is a small tube with a tiny video lens at the end). Further bleeding is a risk after an initial peptic ulcer bleed has been treated.

Prevalence and disease occurrence

Each year, approximately 0.02–0.05% of adults are diagnosed with peptic ulcer bleeding. Recurrence of peptic ulcer bleeding is reported in up to one third of adults after an initial peptic ulcer bleed.

Risk factors

The main risk factors for peptic ulcer bleeding are *H. pylori* infection, history of peptic ulcer and use of NSAIDs (including ASA) and old age. Men are more likely than women to have peptic ulcer bleeding. Factors that increase the risk of repeated bleeding include old age and poor overall health, large ulcer size and ulcer location.

Main treatment options

After successful endoscopic therapy, intravenous PPI therapy (given directly into a blood vessel) and then a once-daily PPI tablet/capsule are recommended to decrease re-bleeding and mortality in high-risk patients.

Mortality and morbidity

About nine in 100 people die within 30 days of a peptic ulcer bleed.

VI: 2.1.4 Zollinger–Ellison syndrome

Disease description

Zollinger–Ellison syndrome (ZES) is a condition in which too much stomach acid is produced, leading to peptic ulcer disease and complications. ZES is caused by a tumour usually in the pancreas or duodenum, called a gastrinoma. Symptoms of ZES include diarrhoea, nausea and vomiting, abdominal pain and GERD symptoms.

Prevalence and disease occurrence

ZES is a rare disease. Each year, approximately one person in two million is diagnosed with ZES. About 0.1% of patients with duodenal ulcer disease have ZES.

Risk factors

ZES is typically diagnosed when patients are aged in their 40s. The disease is caused by gastrinomas, which are tumours in the pancreas or duodenum that release large amounts of the hormone gastrin, leading to the production of too much stomach acid. Gastrinomas may occur sporadically or may be inherited as part of a genetic condition.

Main treatment options

ZES is treated with medications such as PPIs that reduce the amount of acid your stomach produces and surgery if appropriate, to remove tumours. When tumours are too widespread to remove with surgery then sometimes chemotherapy is used.

Mortality and morbidity

Gastrinomas associated with ZES spread to other sites in the body (metastasis) in 10–30% of cases. With PPI treatment, 10-year survival is close to 100% in patients without metastatic disease or with only lymph node metastases, and 30% in those with liver metastases. ZES results in acid-peptic conditions including peptic ulcer disease and severe GERD.

VI: 2.2 Summary of treatment benefits

Esomeprazole belongs to a class of medications called proton-pump inhibitors (PPIs). It works by decreasing the amount of acid made in the stomach. PPIs such as esomeprazole, omeprazole, lansoprazole, pantoprazole and rabeprazole have an important role in the treatment of acid-related diseases and are currently considered the treatment of choice in these conditions. Alternative classes of drugs to treat GERD/symptoms of heartburn are histamine-receptor blockers such as ranitidine and cimetidine, as well as antacids. Omeprazole was the first PPI to be approved more than 20 years ago. Esomeprazole was first approved in 2000 and there has been extensive experience with this medicine since then.

Esomeprazole is used to treat gastroesophageal reflux disease (GERD), a condition in which backward flow of acid from the stomach causes heartburn and possible injury of the oesophagus (the tube between the throat and stomach). Esomeprazole is used to treat the symptoms of GERD, allow the oesophagus to heal, and prevent further damage to the oesophagus. It is also used to treat rare conditions where the stomach produces too much acid, such as Zollinger-Ellison syndrome.

Esomeprazole is also prescribed together with appropriate antibiotics to take away *H. pylori* (a bacteria which is considered important in contributing to doudenal ulcers), to heal doudenal ulcers and prevent peptic ulcers to reoccur. Esomeprazole has also been shown to reduce the risk of developing stomach ulcer in patients who are taking non-steroidal anti-inflammatory agents (NSAIDs; anti-inflammatory painkillers such as ibuprofen); thus, esomeprazole is indicated to prevent these stomach side effects in patients who need to be treated with NSAIDs.

Esomeprazole is also used to prevent re-bleeding in patients with bleeding peptic ulcers that initially have been treated to stop bleeding by endoscopy (tube inserted through mouth/esophagus to stomach).

Esomeprazole comes as a stomach resistant tablet or capsule to take by mouth and in packets of stomach resistant granules (sachet) to be mixed with water taken by mouth or through a feeding tube.

Esomeprazole also comes in a form suitable for injection into a blood vessel, usually in situations when taking esomeprazole by mouth is considered inappropriate or not possible. To prevent re-bleeding of stomach ulcer after therapeutic endoscopy, infusion (drip) of esomeprazole should be administered in hospital for 3 days (72 hours) until treatment with esomeprazole by mouth is started.

Esomeprazole can be prescribed to adults, as well as children aged 1 11 years and 12 18 years.

VI: 2.3 Unknowns relating to treatment benefits

The benefits of esomeprazole are proven and extensive, with no important gaps in knowledge.

VI: 2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and missing information, these are defined as follows:

- ‘Identified risks’ are known side-effects which are included in the SmPC and PIL for esomeprazole. Those side effects which have been deemed as the most severe to the patients have been defined as ‘Important identified risks’ and are presented in Table VI-5 below
- An ‘Important potential risk’ is a condition for which there might be a link with esomeprazole or other medicines which belong to the same group but where a link has not been confirmed
- ‘Missing information’ is information about the safety of a medicine that is not available when the medicine was approved for sale.

VI: 2.4.1 Esomeprazole

Table VI-5 Important identified risks

Risk	What is known	Preventability
Lack of white blood cells **(Agranulocytosis)**	Agranulocytosis during treatment with esomeprazole may affect up to 1/10000 people. This occurs when the bone marrow does not produce enough white blood cells called granulocytes; bone marrow is the soft substance inside bones that forms blood cells. People with less white blood cells have an increased risk of various infections	Yes, by monitoring for early symptoms of infections
Allergic reactions including anaphylactic shock/reaction and tightening of muscles that surround the airways leading to breathing difficulties **(Hypersensitivity reactions)**	Allergic reactions including anaphylactic shock/reaction and bronchospasm (tightening of muscles that surround the airways that can lead to difficulty breathing) during treatment with esomeprazole may affect up to 1/1000 people. These may result in symptoms such as: sudden wheezing, or suddenly feeling wheezy or short of breath, swelling of the lips, tongue and throat or body, rash, fainting or difficulties in swallowing, depending on how serious the reaction is	There is an instruction in the Patient Information Leaflet that people should not take esomeprazole - if they are allergic to esomeprazole or any of the other ingredients of this medicine. - if they are allergic to medicines containing other proton pump inhibitors (eg, pantoprazole, lansoprazole, rabeprazole or omeprazole).
Low levels of magnesium in the blood **(Hypomagnesaemia)**	Low levels of magnesium may result in weakness, being sick (vomiting), cramps, tremor and changes in heart rhythm (arrhythmias). Some patients with low magnesium levels may also have low potassium or calcium levels in the blood	The patient's doctor may wish to measure blood levels if a patient experiences any of the symptoms of low magnesium.

Table VI-5 Important identified risks

Risk	What is known	Preventability
Depression **(Depression)**	Depression during treatment with esomeprazole may affect up to 1/1000 people. Depression affects people in different ways and can cause a wide variety of symptoms. They range from feelings of sadness and hopelessness, to losing interest in the things you used to enjoy and feeling very tearful. People with depression may also have symptoms of anxiety. Depression may cause other symptoms such as feeling constantly tired, sleeping badly, having no appetite or sex drive, and complaining of various aches and pains. The severity of the symptoms can vary. At its mildest, you may simply feel persistently low in spirit, while at its most severe depression can make you feel suicidal and that life is no longer worth living.	Yes, by being aware of the early symptoms of depression
Liver infection with or without yellowing of skin and eyes, liver failure and brain disorder caused by liver failure **(Hepatic reactions)**	Hepatitis, sometimes with jaundice as well, during treatment with esomeprazole may affect up to 1/1000 people. More severe liver problems, including liver failure and brain disorder caused by liver failure, during treatment with esomeprazole may affect up to 1/10000 people. Hepatitis is a term used to describe inflammation (swelling) of the liver. It can occur as a result of a viral	There is an instruction in the Patient Information Leaflet that people should tell their doctor if they notice jaundice or are known to have severe liver disease. Liver failure including brain disorder caused by liver failure, may require admission to hospital. In the hospital the function of the body is supported while medication is given to remove toxins from the blood while the liver recovers

Table VI-5 Important identified risks

Risk	What is known	Preventability
	infection or because the liver is exposed to harmful substances such as alcohol or drugs. The initial symptoms of hepatitis may be similar to those of the flu, and may include muscle and joint pain, a high temperature (fever) of 38°C or above, feeling or being sick, headache, and occasionally yellowing of the eyes and skin (jaundice). Liver failure occurs when large parts of the liver become damaged beyond repair and the liver is no longer able to function. It can be a serious condition that demands urgent medical care. One of the most important functions of the liver is to remove unwanted substances (toxins) from the blood. If the liver is damaged and not working, the levels of toxins in the blood will increase and symptoms of brain disorder such as agitation, confusion, disorientation, muscle stiffness, muscle tremors, difficulty speaking and, in very serious cases, coma can appear	
Severe skin reactions **(Severe cutaneous reactions)**	Erythema multiforme (an inflammatory skin disorder with characteristic skin lesions) and Stevens-Johnson syndrome or toxic epidermal necrolysis during treatment with esomeprazole may affect up to 1/10000 people. Erythema multiforme is a type	Yes, by monitoring for early signs of 'target lesions' and other symptoms of these skin reactions. These severe skin reactions may require admission to hospital for urgent treatment

Table VI-5 Important identified risks

Risk	What is known	Preventability
	of less severe skin reaction that may present with itchy, pink-red blotches, with a 'target lesion' appearance with a pink-red ring around a pale centre. If the cause is stopped, the reaction will often get better within 7–10 days. Stevens–Johnson syndrome (SJS) is a severe skin reaction that usually begins with fever, sore throat, and tiredness. Ulcers and other lesions begin to appear in the mucous membranes lining the mouth and lips but also in the genital and anal regions. Those in the mouth are usually extremely painful and reduce the patient's ability to eat or drink. Conjunctivitis (redness and soreness) of the eyes may also occur. A rash of round lesions about an inch (2-3 cm) may spread across the face, trunk, arms and legs, and soles of the feet. The reaction may then develop into a more severe form with reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. Toxic epidermal necrolysis is considered to be a more severe form of Stevens-Johnson syndrome	

Table VI-5 Important identified risks

Risk	What is known	Preventability
Inflammation within the kidneys **(Interstitial nephritis)**	Interstitial nephritis during treatment with esomeprazole may affect up to 1/10000 people. Interstitial nephritis is a kidney disorder in which the spaces between the kidney tubules become swollen (inflamed). This can cause problems with the way the kidneys work. Interstitial nephritis can cause mild to severe kidney problems, including acute (sudden) kidney failure. Symptoms of this condition may include blood in the urine, fever, increased or decreased volumes of urine, changes in mental status (such as drowsiness, confusion and coma), nausea (feeling sick), vomiting (being sick), rash, swelling of body areas (such as the ankles) and weight gain	Yes, by being aware of early signs and symptoms
Fracture of the hip, wrist or spine	Some population studies have indicated that the use of proton pump inhibitors (like esomeprazole) may be associated with a small increased risk for osteoporotic bone fractures (osteoporosis is a condition where certain bones become brittle). However, other similar population-based studies found no such increased risk. It has not been established that esomeprazole causes fractures	There is an instruction in the Patient Information Leaflet for prescribed esomeprazole that people should tell their doctor if they have been diagnosed with osteoporosis (brittle bone disease)

Table VI-5 Important identified risks

Risk	What is known	Preventability
Infections in the stomach and the gut **(Gastrointestinal infections)**	Treatment with esomeprazole decreases the amount of acid in the stomach that can result in an increased number of bacteria in the stomach and the gut. This can lead to symptoms such as diarrhoea	To be aware of side effects which can be due to infections in the stomach and gut such as severe diarrhoea

Important identified risks (interactions)

Esomeprazole can affect the way some of the following medicines work and these are presented in Table VI-7 below.

Table VI-6 Important identified risks (interactions)

Risk	What is known	Preventability
Drugs used to thin the blood **(Interaction with warfarin or other coumarine derivatives)**	The effect of warfarin (to prevent blood clotting) may be increased if esomeprazole is taken at the same time. This could lead to an increased risk of bleeding	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking drugs to thin the blood. The patient's doctor may need to monitor the patient when start or stop taking esomeprazole
Drug used to treat epilepsy **(Interaction with phenytoin)**	Esomeprazole may slightly increase the concentration of phenytoin in blood. This might lead to more side effects due to the phenytoin, such as dizziness, failure of muscular coordination or eye movement, trembling, increased levels of liver enzymes in the blood, and eyesight problems	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking phenytoin

Table VI-6 Important identified risks (interactions)

Risk	What is known	Preventability
Drug used to treat HIV infection **(Interaction with atazanavir or nelfinavir)**	Omeprazole (another PPI) has been reported to reduce the concentration in the blood of drugs used to treat HIV infection, such as atazanavir and nelfinavir. Therefore, it is likely that this may occur also with esomeprazole. A reduction of the concentration of atazanavir in blood might lead to a reduced effect in patients with HIV	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking medication for the treatment of HIV such as atazanavir or nelfinavir
Drug used for heart problems **(Interaction with digoxin)**	Esomeprazole may increase the concentration of digoxin in the blood. An increase in digoxin levels might lead to more side effects due to the digoxin, such as nausea, vomiting, and heart rhythm disturbances	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking digoxin
A chemotherapy medicine used to treat cancer and rheumatic disorders **(Interaction with methotrexate)**	Esomeprazole may increase the concentration of methotrexate in the blood especially if methotrexate is given in high doses. An increase in methotrexate levels might lead to more side effects due to the methotrexate, such as kidney failure, decreased production of blood cells, decreased liver function, severe skin reactions and lung disorders	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking methotrexate

Table VI-6 Important identified risks (interactions)

Risk	What is known	Preventability
A drug used in patients with organ transplantation **(Interaction with tacrolimus)**	Esomeprazole may increase the concentration of tacrolimus in the blood. An increase in tacrolimus levels might lead to more side effects due to the tacrolimus, such as increased risk of infections, increased risk of coronary artery disease (narrowing of the small blood vessels that supply blood and oxygen to the heart), anaemia, a decrease in the number of white blood cells and platelets, decreased kidney function, allergy and severe skin reactions	There is an instruction in the Patient Information Leaflet that people should tell their doctor or pharmacist if they are taking tacrolimus
A drug used to prevent blood clots **(Interaction with clopidogrel)**	Esomeprazole (and other proton pump inhibitors eg, lansoprazole and omeprazole) may decrease the concentration of the active piece of clopidogrel in the blood. This might lead to less capacity in preventing blood clots. However, the consequences for the patients are uncertain	There is an instruction in the Patient Information Leaflet that people should specifically tell their doctor or pharmacist if they are taking clopidogrel

Important potential risks

Table VI-7 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Contraction of the body muscles resulting in an uncontrolled shaking of the body **(Convulsion/seizure)**	Symptoms of convulsion/seizure may vary. It is often associated with a sudden and involuntary contraction of a group of muscles and loss of consciousness. However, it can also be as simple as a temporary numbness of a part of the body, a short or long term loss of memory, changes in vision, smelling an unpleasant odor, a strange sensation in the abdomen, or a sensation of fear and confusion. Convulsions/seizure has been described for some patients taking esomeprazole and.
Infection of the lung **(Pneumonia)**	Pneumonia is an inflammatory condition of the lung, usually caused by infection with viruses and bacteria. Typical symptoms include cough, chest pain, fever and difficulty breathing. Treatment depends on the underlying cause, if the pneumonia is caused by bacteria the treatment is antibiotics. Pneumonia can be a severe condition in babies, old people and people with other diseases such as heart, respiratory, liver, and kidney diseases. If the pneumonia is severe, the affected person is generally admitted to hospital. It has been presented in some medical articles that there can be an increased risk for pneumonia in patients who are taking medicines to treat increased acid levels in the stomach.

Areas of Missing information

Table VI-8 Missing information

Risk	What is known
Use in pregnant and breast-feeding women (Use in pregnant and lactating women)	There is a moderate amount of information about use of esomeprazole in pregnant or breast feeding women. However, information from marketed use is continuously collected and evaluated by AstraZeneca and no increased risk for birth defects has been found

Table VI-8 Missing information

Risk	What is known
Use in patients with decreased kidney function (Use in patients with renal impairment)	No specific studies have been done in patients with decreased kidney function. However, there is no reason to believe that esomeprazole would cause any harm in this patient group. The dosing recommendation is the same as for patients with normal kidney function

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

There are no additional risk minimisation measures.

VI: 2.6 Planned post authorisation development plan

There are no planned additional PhV studies or activities.

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

Table VI-9 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety Concerns	Comment
Important identified risks			
8	19 March 2012	'Hypomagnesaemia'	Hypomagnesaemia was included as an 'Important identified risk'
8.1	February 2013	'Fracture of the wrist, hip or spine'	Fracture of the hip, wrist or spine is included as an 'important identified risk'. It was included as an uncommon ADR in the SmPCs for esomeprazole with (imposed).

Table VI-9 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety Concerns	Comment
8.3	May 2013	Gastrointestinal infections	'Gastrointestinal infections ' was included as an 'Important identified risk' as per request by European Medicines Agency
Important identified interactions			
Not applied	November 2009	'Interaction with nelfinavir'	'Interaction with nelfinavir' was included as an important identified interaction
Not applied	November 2009	'Interaction with clopidogrel'	'Interaction with clopidogrel' was identified as a potential interaction and included in the EU RMP
7	15 April 2011	'Interaction with digoxin'	'Interaction with digoxin' was included as an 'Important identified interaction'
8	19 March 2012	'Interaction with methotrexate'	'Interaction with methotrexate' was included as an 'Important identified interaction'
8	19 March 2012	'Interaction with tacrolimus'	'Interaction with tacrolimus' was included as an 'Important identified interaction'

Table VI-9 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety Concerns	Comment
8	19 March 2012	'Interaction with clopidogrel'	'Interaction with clopidogrel' was included as an 'Important identified interaction'
Important potential risks			
8	19 March 2012	'Convulsion/seizure'	'Convulsion/seizure' included as an 'Important potential risk'
8.1	February 2013	'Use of acid-suppressing drugs during pregnancy and childhood asthma'	Use of acid-suppressing drugs in pregnancy and childhood asthma included as an 'Important potential risk'
8.4	June 2013	Pneumonia	As per request by European Medicines Agency during the regulatory review process for esomeprazole non prescription use in EU, Pneumonia 'was included as an 'Important Potential Risk'.
11	June 2015	'Use of acid-suppressing drugs in pregnancy and childhood asthma'	Use of acid-suppressing drugs in pregnancy and childhood asthma removed as an 'Important potential risk'

Table VI-9 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety Concerns	Comment
Missing information			
12	February 2016	‘Long-term treatment in children’	‘Long-term treatment in children’ removed as ‘Missing information’,
8.3	May 2013	‘Use in pregnant and lactating women’	‘Pregnant and lactating women’was included as 'Missing information' as per request by European Medicines Agency
8.3	May 2013	‘Use in patients with renal impairment’	'Renal impairment' was included as 'Missing information' as per request by European Medicines Agency

VI: 3 GLOSSARY

Antacids – medications that neutralize stomach acid

Barrett's esophagus - condition in which the cells of lower esophagus become damaged

Complicated ulcer – an ulcer associated with intestinal bleeding or perforation (puncture)

Diaphragm – the muscle that separates the belly from the chest

Duodenal ulcer – a break in the lining of the duodenum that looks like a sore

Duodenum – the first part of the small intestine

Gastric ulcer – break in the lining of the stomach that looks like a sore

Gastrinoma – a tumour in the pancreas or duodenum that releases large amounts of the hormone gastrin, leading to the production of too much stomach acid

Gastroesophageal reflux disease (GERD) – a condition in which stomach contents leak back up into the oesophagus, causing GERD symptoms (such as heartburn and regurgitation) and complications (such as reflux oesophagitis)

Heartburn – an uncomfortable burning sensation in the chest

H. pylori – a bacterium that infects the stomach lining, causing gastric and duodenal ulcers

Hiatus hernia – a condition in which the upper part of the stomach protrudes upwards through the diaphragm

Histamine-receptor blockers – drugs that partially block acid production in the stomach

Lower oesophageal sphincter – the ring of muscles at the lower end of the oesophagus where it meets the stomach

Metastasis – spread of tumours to other parts of the body

Oesophagus – the tube from the mouth to the stomach

Peptic ulcer – a gastric or duodenal ulcer

Prokinetic agents – drugs that increase gastrointestinal movement

Proton pump inhibitors (PPIs) – drugs that block acid production in the stomach

Regurgitation – a sensation of movement of stomach contents up towards the throat or mouth

Reflux oesophagitis – inflammation or damage to the lining of the oesophagus caused by refluxed acid from the stomach

Uncomplicated ulcer – an ulcer that is not associated with gastrointestinal bleeding or perforation (puncture)

Zollinger–Ellison syndrome (ZES) – a condition in which too much stomach acid is produced, leading to severe GERD and peptic ulcer disease.