## 6.2 Elements for a public summary

### *6.2.1 Overview of disease epidemiology*

*Epidemiology of gastro-oesophageal reflux disease (GERD)and Reflux oesophagitis*

Epidemiological studies of gastro-oesophageal reflux disease (GORD) are confounded by the lack of a standardized definition and a diagnostic 'gold-standard' for the disorder[4]. When defined as at least weekly heartburn and/or acid regurgitation, the occurrence in the Western world generally ranges between 10% and 20% whereas in Asia the occurrence is reported to be less than 5%. There is a trend for the occurrence in North America to be higher than that in Europe, and a trend is also suggested for a higher occurrence in Northern over Southern Europe[7]. In Western countries, 20-40% of the adult population experience heartburn, which is the important symptom of GORD, but only some 2% of adults have objective evidence of reflux oesophagitis. The incidence of GORD increases with age, rising dramatically after 40 years of age. There is also wide geographical variation in prevalence[4].

According to Wienbeck et al, the prevalence of reflux esophagitis in Western countries is estimated to be 2% and that of reflux disease 5%. The main complications of reflux esophagitis are Barrett's esophagus, peptic stricture, ulceration and bleeding[5].

As per Hongo M, In East Asia, prevalence of reflux esophagitis is between that of Western Europe and Africa. The prevalence of columnar-lined esophagus (CLE) was surveyed in East Asia and in Sendai, with reference to Helicobacter pylori infection. Prevalence of CLE was 0.9% in East Asia and 1.2% in Sendai, and H. pylori infection was 4% and 20%, respectively. Patient mean age was 63 years, and 73% were male. Endoscopic severity of esophagitis was mild[6].

Data from the studies referred, indicate that obesity and possibly increasing age are risk factors for GORD, although sex is not. These data imply that a genetic component exists in the development of GORD, exerting influence beyond that of any shared familial environmental factors. The most commonly factors which trigger gastro-oesophageal reflux episodes were cigarette smoking and coffee consumption[7]. Complications, including oesophageal ulcer and stricture, and Barrett's oesophagus, are found in up to 20% of patients with verified reflux oesophagitis. The signs and symptoms of GORD often wax and wane in intensity, and spontaneous remissions have been reported. In most cases, however, GORD is a chronic condition that returns shortly after discontinuing therapy. Although GORD causes substantial morbidity, the annual mortality rate due to GORD is very low (approximately 1 death per 100,000 patients), and even severe GORD has no apparent effect on longevity, although the quality of life can be significantly impaired[4]. GORD, defined as symptoms likely to impair quality of life, affects up to 20% of the Western population and is associated with a range of risk factors[7].

*Epidemiology of Gastric and duodenal ulcer*

Factors that increase the risk of serious peptic ulcer disease include older age, history of peptic ulcer disease, gastrointestinal hemorrhage, dyspepsia, and/or previous NSAID intolerance, as well as several measures of poor health[8]. Peptic ulcer disease (PUD) is an important cause of morbidity and health care costs; estimates of expenditures related to work loss, hospitalization, and outpatient care (excluding medication costs) are $5.65 billion per year in the United States[9].
A study conducted by Saeed Hamid et al concluded that NSAID-associated peptic ulcer disease is common in Pakistan and most frequently associated with gastric and duodenal ulcer. H. pylori infection is common in association with NSAID related peptic ulcers (JPMA 56:218;2006).[10]
Since the mid-twentieth century peptic ulcer mortality in Westernised countries has declined in young and middle aged subjects. Ulcer mortality in senior citizens has, none the less, remained essentially unchanged or even increased.[11]

Use of the majority of NSAIDs increases with age, primarily for symptoms associated with osteoarthritis and other chronic musculoskeletal conditions. NSAIDs cause a wide variety of side-effects. The most clinically important side-effects are upper gastrointestinal tract dyspepsia, peptic ulceration, hemorrhage, and perforation, leading to death in some patients. Many studies have shown that NSAIDs increase the risk of peptic ulcer complications by 3-5-fold, and in several different populations it has been estimated that 15-35% of all peptic ulcer complications are due to NSAIDs.

One study conducted by S J Rosenstock and T Jorgensen, showed Life time ulcer prevalence (95%/o confidence intervals) was 5.6 (4.9-6.4) per cent. Male to female prevalence ratio was 22:1, and duodenal to gastric ulcer prevalence ratio was 3.8:1. Thirty two participants with no previous history of peptic ulceration developed an ulcer within the observation period resulting in a five year ulcer incidence of 11.3 (7.4.15.2) per 1000 persons at risk with no demonstrable sex difference. The prevalence of duodenal ulcer has declined in Denmark whereas gastric ulcer prevalence in men has increased slightly[11].

A study conducted by Marcel JM Groenen et al showed that 20,006 upper gastrointestinal endoscopies were performed. Duodenal ulcers were diagnosed in 696 (3.5%) cases, with signs of bleeding in 158 (22.7%). Forty-five (6.5%) of these ulcers were classified as Forrest I and 113 (16.2%) as Forrest II. Gastric ulcers were diagnosed in 487 cases (2.4%), with signs of bleeding in 60 (12.3%). A Forrest 1 designation was diagnosed in 19 patients (3.9%) and Forrest 2 in 41

patients (8.4%). The incidence of gastric ulcers was stable over time, while the incidence of duodenal ulcers declined[12].

The Authors concluded that the incidence of uncomplicated peptic ulcer disease, especially for duodenal ulcers, has declined in the Western population. However, the incidence of complicated ulcer disease is rising, which underlines the need to be more alert in providing patients using NSAIDs with adequate gastroprotection to prevent ulcer disease and its complications[12].

*Epidemiology of Zollinger-Ellison-Syndrome*

Zollinger-Ellison syndrome (ZES) is caused by a non–beta islet cell, gastrin-secreting tumor of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity, with consequent gastrointestinal mucosal ulceration. ZES may occur sporadically or as part of an autosomal dominant familial syndrome called multiple endocrine neoplasia type 1 (MEN 1). The primary tumor is usually located in the duodenum, the pancreas, and abdominal lymph nodes, but ectopic locations have also been described (eg, heart, ovary, gall bladder, liver, kidney).
ZES occurs in approximately 0.1-1% of all patients with duodenal ulcers. Its frequency of occurrence is reported to be approximately the same as insulinoma, the most common functioning pancreatic endocrine tumor. 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. The mean age of onset of ZES is 43 years, with the patients with MEN 1/ZES presenting a decade earlier. Generally, a 5- to 7-year delay in diagnosis occurs. In a recent prospective study, fewer than 3% of patients were younger than 20 years, while 7% were older than 60 years at the time of disease onset. Currently, the morbidity and mortality of ZES is low because of improved medical and surgical management of the disease. Fewer than 5% of patients develop a complication, such as abdominal perforation, gastric outlet obstruction, or esophageal stricture. All races can be affected. A slight male predominance exists, with a male-to-female ratio of 1.3:1[13].

### *6.2.2 Summary of treatment benefits*

In a study conducted by Jungnickel PW, Intravenous pantoprazole has been assessed in 269 patients for the treatment of gastric or duodenal ulcer, reflux oesophagitis or other gastrointestinal disease. Pantoprazole 40 mg/day was administered to 94.7% of patients, 20 mg/day was administered to 5%, and 80 mg/day was administered to 0.3%. Treatment outcomes were assessed at the end of i.v.

therapy in 262 patients, 90% of whom had received ≤ 10 days of treatment. Review of this study highlights complete healing in 7.3% of patients, with 70.2% judged significantly improved, 14.5% slightly improved, 7.6% unchanged, and 0.4% worse20. Thus, intravenous pantoprazole is beneficial for hospitalized patients who cannot take oral medications[14].

### *6.2.3 Unknowns relating to treatment benefits*

No or very limited information is available regarding treatment benefits of Pantoprazole in Paediatric patients. There are no adequate and well controlled studies in pregnant or lactating women.

### *6.2.4 Summary of safety concerns*

The most common side effects with pantoprazole SUN are diarrhea, abdominal pain, chest pain, rash, flatulence (gassiness) and headache.

Pantoprazole SUN must not be used in people who are hypersensitive (allergic) to pantoprazole. It must not be used with atazanavir (a medicine used to treat human-immunodeficiency-virus [HIV] infection).

Malignancy should be ruled out in case of alarming symptoms (e.g. significant unexpected weight loss, recurrent vomiting, dysphasia), as treatment with pantoprazole SUN may alleviate symptoms and results in disease progression/delayed diagnosis.

In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued.

Events like dizziness, vision disturbances, blurred vision have been reported to occur, skillful activities like driving, use of machine shall be avoided while on pantoprazole therapy.

A summary is given in table below and a full list of all side-effects is available in the SPC:

| Identified Risk | Known Information | Preventability |
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| Hypersensitivity to pantoprazole or other substituted benzimidazoles | Anaphylactic shock has been reported to occur within a few minutes after intravenous pantoprazole use.<br>Rare cases of anaphylaxis, angioedema, and severe dermatologic reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis--some | Pantoprazole SUN must not be used in people who are hypersensitive (allergic) to pantoprazole, or to any other benzimidazoles medication such as albendazole, or mebendazole. |

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| | fatal--and erythema multiforme) have been described in post marketing reports. | Intravenous use and hospital administration under appropriate medical supervision ensures immediate diagnosis and proper management in case of anaphylaxis. |
| Long-term treatment with PPI's and hypomagnesaemia | Severe hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. | Magnesium replacement and discontinuation of the PPI is recommended. 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 treatment.<br>It seems appropriate to do routine testing to monitor calcium, vitamin B12, magnesium and iron levels in long term PPI users. |
| 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 should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.<br><br>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.<br><br>Postmenopausal women, patients with osteoporosis, elderly patients and people at high risk of fall should be |

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| | | treated carefully. |
| Visual disturbances | Disturbances in vision/ blurred vision are rarely reported during post-marketing surveillance. | Patients should be warned against driving or performing skillful activities. |
| Malabsorption of vitamin B12 (cyanocobalamine): | Gastric acid and pepsin are essential in order to release cobalamine (precursor of vitamin B12) from dietary proteins. Rare reports of cyanocobalamine (vitamin B12) deficiency have been reported with acid-suppressing therapy. Patients receiving acid suppressing therapy over a long period of time (e.g., longer than 3 years) may be at risk of cyanocobalamine malabsorption caused by hypo- or achlorhydria. | Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.<br><br>It seems appropriate to do routine testing to monitor calcium, vitamin B12, magnesium and iron levels in long term PPI users. |
| *Important potential risks* | | |
| Tumorigenicity | Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown. One report of carcinoid tumour of the stomach have been reported in post-marketing surveillance [long term therapy (10+ years) with PPI].<br><br>The persistent inflammation caused by H. pylori may lead to the development of atrophic gastritis and intestinal metaplasia, conditions at increased risk of gastric cancer. | Patients should be prescribed the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.<br><br>Further investigations to be considered in case of alarming symptoms or persistent symptoms despite adequate treatment.<br><br>Close monitoring of long term use of pantoprazole.<br><br>H. pylori testing should be done prior to initiation of chronic PPI therapy |
| Increased risk of Clostridium difficile- | Treatment with proton pump inhibitors may lead to slightly | Patients should use the lowest dose and shortest |

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| associated diarrhea with PPI's | increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.<br><br>PPIs are possibly associated with increased incidence of Clostridium difficile-associated diarrhea (CDAD). | duration of PPI therapy appropriate to the condition being treated.<br><br>A diagnosis of Clostridium Difficile Associated Diarrhea should be considered for Pantoprazole users with diarrhea that does not improve. |
| Congenital cardiac malformation following in utero exposure | In 2010, two studies did raise concerns about the use of proton pump inhibitors in expectant mothers. The first, conducted at the University of Pennsylvania and published in the journal Gastroenterology, drew data on 200,000 pregnant women from the Health Improvement Network (THIN) database. Out of the 208,951 pregnancies recorded, there were 2,445 cases of cardiac birth defects. The study found that taking proton pump inhibitors in early pregnancy was associated with a doubling in the risk of newborn cardiac birth defects, such as septal defect. The study was presented at the Digestive Disease Week Conference May 1-5, 2010.<br>The second study, this time out of Denmark and published in the New England Journal of Medicine, suggested that the number of children with birth defects born to women taking proton pump inhibitors was not statistically significant. However, the same study also found that women who took the medications in the four | 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 SUN 40 mg should not be used during pregnancy unless clearly necessary. |

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| | weeks leading up to pregnancy had a 39 percent greater risk of having children with birth defects. | |
| Decrease in absorption of iron | Gastric acid greatly improve the absorption of non-heme iron (66% of dietary iron) by dissociating the iron salts from the food source and helping them to be reduced to the ferrous state, so it can bind to ascorbate, sugars and amines to be absorbed.<br>It is already known that iron-deficiency anemia results from conditions with low or no gastric acid such as atrophic gastritis, pernicious anemia or gastric resections. | Concurrent PPIs and oral iron supplement may cause malabsorption of iron, thus close monitoring is warranted. |
| Off-label use | Off-label use of pantoprazole can be in following indications stress-related mucosal disease, NSAID-induced ulcer prophylaxis, stress gastritis prophylaxis, the eradication of H Pylori infection in combination with antibiotics, use in children and long term use of more than one year. | Professional labelling.<br><br>Shortest duration of PPI therapy appropriate to the condition being treated. |
| Interstitial nephritis leading to renal failure | Few isolated case reports have been received for interstitial nephritis, increased creatinine, allergic henoch schonlein purpura, acute renal failure associated with Pantoprazole use. In most of the cases either the patient was on drugs known to cause renal damage (alone or in combination) or having risk factor for the development of renal failure. | Patients should be prescribed the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.<br>Early Discontinuation of pantoprazole in case of deranged renal function profile to be considered, to prevent further progression,<br><br>Caution should be exercised while prescribing pantoprazole in the patient having risk factors for the development of renal failure |

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| | | including those on drugs known to cause renal damage. |
| Acute Pancreatitis | Rare cases of pancreatitis have been described in post-marketing reports. However, a causal relationship has not been established. | Patients should be prescribed the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. |
| Hepatocellular damage leading to jaundice and hepatic failure. | Sporadic reports of increased liver enzymes, increased bilirubin, Hepatocellular injury, jaundice and hepatocellular failure have been reported in post-marketing surveillance. | In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued. |
| Atrophic gastritis | Long term acid suppression may lead to the development of atrophic gastritis which could be a precursor of cancer.<br>Atrophic gastritis has been observed occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were Helicobacter pylori positive. | Patients should be prescribed the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. |
| Chronic use of PPIs and the risk of Pneumonia | Patients receiving PPIs, particularly <30 days or high dose, showed an association with community-acquired pneumonia.A causal relationship has not been established 1.<br>PPIs appear to be associated with increased risk of GI infections and pneumonia especially in patients with concomitant risk factors such as hospitalization and multiple antibiotics | Patients should be prescribed the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.<br><br>Practitioners need to be vigilant about such adverse effects of PPIs and avoid long term use. |
| Potential interaction with Methotrexate | There is evidence to suggest that concomitant use of methotrexate | Physicians should be alerted to this potential drug-drug |

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| | (primarily at high doses) with PPIs such as omeprazole, esomeprazole, and pantoprazole may decrease methotrexate clearance (by decreasing renal clearance) , leading to elevated serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities[2]. | interaction in patients receiving concomitant high-dose methotrexate and PPIs. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients |
| Potential interaction with drugs metabolised by the cytochrome P450 system | Pantoprazole is extensively metabolised by hepatic P450 enzyme CYP2C19; second pathway through CYP3A4. There is theoretical risk of interactions with drugs also metabolized with these pathways.<br><br>About 3 % of Caucasians (or Europeans) and African Americans are deficient in CYP219 enzyme system (poor metabolisers). Plasma concentration can increase 5 times or more in poor metabolisers as compared to those having a functional CYP2C19 enzyme (extensive metabolisers). | Interaction studies with drugs also metabolized with these pathways, did not reveal clinically significant interactions. However, monitoring is advised particularly in intermediate or poor metabolisers of CYP2C19.<br><br>Poor metaboliser status has no implications for the posology of pantoprazole. As systemic exposure with up to 240 mg administered intravenously over 2 minutes were well tolerated. However, these individuals are more prone to pantoprazole overdose/toxicity. |
| Potential interference with diagnostic test results | There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors.<br><br>Decreased gastric acidity increases serum chromogranin A (CgA) levels and may cause false-positive diagnostic results for neuroendocrine tumors. | An alternative confirmatory method should be considered to verify positive results.<br><br>Temporary discontinuation of PPIs before assessing CgA levels is advised.<br><br>Testing for Helicobacter |

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| | Proton pump inhibitors may interfere with the detection of Helicobacter pylori by the urea breath test. | pylori with the urea breath test is not recommended in patients who have received proton pump inhibitors in the preceding two weeks. |
| Potential interaction with medicinal products with pH dependent absorption. | Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib. | Concomitant use of such medications should be avoided.<br>If unavoidable, dose adjustments of concomitant drugs or temporary interruption of pantoprazole therapy should be considered based on the clinical need under guidance of treating physician. |
| Potential interaction with Coumarin anticoagulants (phenprocoumon or warfarin) | A few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. | In patients treated with coumarin anticoagulants monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole. |
| Potential interaction with HIV medications (atazanavir, rilpivirine, nelfinavir) | 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. | The co-administration of proton pump inhibitors with atazanavir is not recommended). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical 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. |
| Potential interaction with Phenytoin | Pantoprazole inhibits oxidative hepatic metabolism of | Concomitant use shall be avoided. |

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| | Phenytoin, decreases it's plasma clearance by 15% and increases it's elimination half life by 27%, resulting in higher serum levels.<br>Pantoprazole is a CYP3A4 inducer and a weak CYP2C19 inhibitor. | |
| Potential interaction with Digoxin | Concomitant use of PPIs with Digoxin may cause hypomagnesaemia<br>Proton pump inhibitors including pantoprazole may increase the effects of digoxin. In the short-term, pantoprazole can occasionally cause an increase in the blood levels of digoxin.<br><br>Prolonged concomitant use may lead to Hypomagnesemia, which can increase the sensitivity of heart to the effects of digoxin and cause toxicity even if your digoxin levels are within range. | Concomitant use shall be avoided, may need a dose adjustment or more frequent monitoring by doctor to safely use both medications if such an use in unavoidable.<br><br>Immediate medical attention in case of signs and symptoms indicating excessive effects of digoxin, such as nausea, vomiting, diarrhea, loss of appetite, visual disturbances (blurred vision; light halos around objects; green or yellow vision), or an abnormally fast or slow or uneven heartbeat. |
| Potential interaction with tacrolimus | Using pantoprazole together with tacrolimus may cause a condition called hypomagnesaemia, or low blood magnesium.<br><br>In severe cases, hypomagnesaemia can lead to irregular heart rhythm, palpitations, muscle spasm, tremor, or seizures. Additionally, pantoprazole may increase the blood levels of tacrolimus in some people. This may increase the risk of serious | Concomitant use shall be avoided. Other alternatives which do not interact can be considered.<br><br>May need a dose adjustment or more frequent monitoring by doctor to safely use both medications if such an use is unavoidable. |

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| | side effects such as diabetes, infections, kidney damage, high blood potassium (hyperkalemia), tremor, seizures, visual disturbances, high blood pressure, and heart enlargement. | |
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| **Missing information** | | |
| Use in pregnancy | There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown. | Pantoprazole SUN 40 mg should not be used during pregnancy unless clearly necessary |
| Use in Lactation | Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. | A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantoprazole SUN 40 mg should be made taking into account the benefit of breast-feeding to the child and the benefit of Pantoprazole SUN 40 mg therapy to woman. |
| Use in Paediatric patients | The experience in children is limited. | Pantoprazole SUN 40 mg is not recommended for use in patients below 18 years of age until further data become available. |

### *6.2.5 Summary of additional risk minimisation measures by safety concern*
*Not applicable*

### *6.2.6 Planned post authorisation development plan*
Not applicable

### *6.2.7 Summary of changes to the risk management plan over time*

Not applicable since this is the initial version