13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Nausea and Vomiting caused by Cancer Chemotherapy (CINV)

Medicines used to treat cancer can cause nausea and vomiting, also known as CINV (chemotherapy-induced nausea and vomiting). Cancer treatment guidelines recommend treatment to prevent or lessen CINV. How commonly CINV occurs depends mostly on the type and dose of cancer drugs used. It has been estimated that in 2016, approximately 1241100 cancer patients will be treated with chemotherapy in France, Germany, Italy, Spain and the United Kingdom. Of these patients, three-fourths would be at risk for CINV.

In addition to the risk of CINV from the cancer medicines themselves, patients who are younger, female, and those with previous motion sickness are more likely to have CINV.

Current treatments to prevent CINV include serotonin receptor antagonists (ondansetron, granisetron, dolasetron, tropisetron, palonosetron), neurokinin receptor antagonists (aprepitant and fosaprepitant), dopamine receptor antagonists (metoclopramide and prochlorperazine) and corticosteroids (dexamethasone). These medications are given alone or in combination to prevent or treat CINV.

Nausea and Vomiting caused by Cancer Radiation therapy (RINV)

Nausea and vomiting caused by radiation therapy, also known as RINV (radiation induced nausea and vomiting) has been observed in 50-80% of the patients undergoing radiotherapy according a study. Patients undergoing abdominal radiotherapy are at higher risk followed by those treated on thorax, brain, head and neck, and pelvis. It is also noted that patients less than 60 years old are at higher risk of RINV.

Current treatment for RINV is similar to that of CINV, which include serotonin receptor antagonists (ondansetron, granisetron, dolasetron, tropisetron, palonosetron), neurokinin receptor antagonists (aprepitant and fosaprepitant), dopamine receptor antagonists (metoclopramide and prochlorperazine) and corticosteroids (dexamethasone). These medications are given alone or in combination to prevent or treat CINV. The available evidence from the clinical studies indicates that 5-hydroxytryptamine (5-HT3) receptor antagonists are the most active agents that have been evaluated in randomized trials.

RINV if not treated, negatively impacts the patients' quality of life and leads to poor compliance for the treatment.

Nausea and Vomiting following Surgery

Nausea and vomiting after surgery, also known as PONV (post-operative nausea and vomiting) is a common side effect after anesthesia, occurring in almost one-third of patients overall during the 24 hours after surgery.

In a study published in 2008, there were approximately 32 million surgeries in France, Germany, Spain, Italy and United Kingdom.

Risk factors for nausea and vomiting after surgery include: being a female who is past puberty, not smoking, and history of motion sickness. Children are twice as likely to have vomiting as adults, and a long surgery also increases the risk of vomiting.

Classes of medicines commonly used for PONV include anticholinergics, antihistamines, phenothiazines, sedatives/anxiolytics, butyrophenones, dopamine antagonists, serotonin receptor antagonists, and corticosteroids, alone or in combination.

PONV almost always goes away with time. Serious complications are rare, although it can cause dehydration, problems healing, bleeding, damage to the throat, and difficulty breathing.

13.2.2 Part VI.2.2 Summary of treatment benefits

Nausea and Vomiting caused by Cancer Chemotherapy/Radiotherapy (CINV/RINV)

CINV/RINV can significantly affect a patient's quality of life, leading to poor compliance with further cancer treatment. Nausea and vomiting can also result in patients having poor nutrition, having difficulty taking care of themselves, or being unable to do things (physically or mentally) as well as they used to. Other complications include poor wound healing and injury to the oesophagus (Ettinger et al 2012). The current gold standard of treatment to prevent acute nausea and vomiting following HEC is a three-drug regimen including single doses of a 5-HT_3 receptor antagonist (such as dolasetron, granisetron, ondansetron, tropisetron), dexamethasone, and aprepitant given before chemotherapy (Roila et al 2010). It is generally agreed that no differences between the serotonin receptor antagonists (dolasetron, granisetron, ondansetron, and tropisetron) exist in terms of efficacy (Roila et al 2010).

Nausea and Vomiting following Surgery

Nausea and vomiting are among the most common complaints after surgery. Severe retching and vomiting is uncomfortable and may result in serious complications or longer stays in the hospital. Patients considered at high risk for nausea and vomiting after surgery are often given medications such as ondansetron before the operation in order to decrease the chance of nausea and vomiting after surgery (Kovak et al 1999).

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The treatment benefits of ondansetron apply to patients with nausea and vomiting due to chemotherapy or radiotherapy and to patients with nausea and vomiting following surgery.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
Very low blood pressure and loss of consciousness when ondansetron is taken at the same time as apomorphine, which is a medicine used in the treatment of Parkinson's	Ondansetron and apomorphine may interact and cause very harmful effects. Using these medicines together may cause very low blood pressure, dizziness, lightheadedness, or loss of	Patients should not take ondansetron and apomorphine together.

Risk	What is known	Preventability
disease (Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride)	consciousness.	
Allergic Reaction (Hypersensitivity)	Severe allergic reactions, including anaphylactic reactions, have been reported with ondansetron treatment. Signs of serious allergic reactions can include rash, hives, swelling of the face, mouth and/or tongue, and breathing problems.	Patients should not take ondansetron if they are allergic (hypersensitive) to ondansetron or any of the other ingredients in the drug product and should be cautious if they are allergic to medicines in the same family as ondansetron.
Heart rhythm problems (QT interval prolongation and Torsade de Pointes)	Ondansetron may increase (prolong) the QTc interval. The QTc interval is one of many pieces of information read from an electrocardiogram (ECG). An ECG is an instrument that measures the electrical activity of the heart. If the QTc interval is increased to the point of causing abnormal heart beats, a patient may experience symptoms. In some cases, this can result in a sensation of palpitations – extra, skipped, or rapid heartbeats. If a patient experiences many extra heart beats in a row (the heart is beating too fast), too little blood gets pumped out of the heart and to the rest of the body, including the brain. This can lead to symptoms of lightheadedness, fainting, or in the most severe form, cardiac arrest requiring defibrillation with electrical pads. In a study in healthy people that was designed specifically to determine the effect of ondansetron on the QTc interval, the effects on QTc interval were related to the amount of ondansetron in the blood. At the highest dose tested (32 mg given into a vein), QTc changes of concern (greater than 10 msec prolongation) were observed. These changes resolved within 3 hours. The 8 mg dose given into a vein did not cause QTc changes of	Because 32 mg given into a vein is known to cause changes in the QT interval that are of concern, this dose should not be used. Certain conditions can result in a patient having a higher risk of abnormal heart beats, including (but not limited to) some of the following – conditions present since birth such as Congenital Long QT Syndrome, problems with salt concentrations in the body (low levels of magnesium, potassium, or calcium in the blood), various types of heart disease, and certain medications that can cause further increases in the QTc interval. Ondansetron should be used cautiously in these situations.

Risk	What is known	Preventability
	concern. GSK has received reports of prolonged QTc interval and rapid heartbeats in patients taking ondansetron, including low doses of ondansetron. Some of these reports described life-threatening or fatal events.	
Severe skin reaction with blisters and loss of skin layers (Toxic epidermal necrolysis)	Toxic epidermal necrolysis (TEN) is a rare, sometimes life-threatening skin condition. Blisters can cover most of the body and the skin can also peel off and expose the underlayers of skin. Because of the skin damage, the patient can more easily develop bad infections. Reactions to drugs have been reported to cause most cases of TEN (Schwartz et al 2013)	Patients with a history of TEN must avoid the drug that caused TEN, as well as medicines that are chemically related.

Table 13-6 Important potential risks

Risk	What is known
Severe side effects on muscles and brain from too much serotonin (Serotonin syndrome)	Serotonin syndrome occurs when you take medications that cause high levels of the chemical serotonin to accumulate in your body. Serotonin syndrome can occur when you increase the dose of such a drug or add a new drug to your regimen. Similar cases were reported with oral overdose of ondansetron in children. Serotonin is a chemical your body produces that is needed for your nerve cells and brain to function. High levels of serotonin may cause symptoms that can range from mild (shivering and diarrhea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can be fatal if not treated (Iqbal et al 2012). Patients should tell their doctor, nurse or pharmacist about all medicines that they are taking, have recently taken or might take. This includes medicines used to treat depression and/or anxiety, including SSRIs (selective serotonin reuptake inhibitors) such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram or SNRIs (serotonin noradrenaline reuptake inhibitors) such as venlafaxine or duloxetine.
Birth defects or other adverse effects on infant if mother takes ondansetron while pregnant (Adverse birth outcomes following use during pregnancy)	Pregnant women have not been included in studies of ondansetron. As a result there is very limited data on the safety of ondansetron for pregnant women and their babies. The use of ondansetron during pregnancy is not recommended.
High blood levels of ondansetron and greater chance of side effects in	Ondansetron is removed from the body by the liver. If you have liver disease, the level of ondansetron in your blood

Risk	What is known
patients with liver disease (Reduced clearance and prolonged half-life in patients with hepatic impairment)	may get too high and increase the chance of side effects. Patients should tell their doctor if they have liver disease.
Slow down or stopping of intestines in patients whose intestines work slowly (Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility)	Ondansetron may slow down how quickly food goes through the intestines. Patients whose intestines work slowly or who have problems with constipation should tell their doctor and may need to be watched closely if they receive ondansetron.
Side effects on breast-fed baby if mother is taking ondansetron (Adverse events in breast-fed infants due to use of ondansetron during lactation)	It is not known if ondansetron gets into mother's breast milk. If ondansetron is present in mother's breast milk, it may cause adverse effects in a breast-fed baby. Your doctor will decide if you should continue taking ondansetron while breastfeeding.

Table 13-7 Missing information

Risk	What is known
Adverse effects on mother if mother takes ondansetron while pregnant (Safety in pregnant women)	Pregnant women have not been included in studies of ondansetron. As a result there is very limited data on the safety of ondansetron for pregnant women. The use of ondansetron during pregnancy is not recommended.

13.3 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures

13.4 Part VI.2.6 Planned post authorization development plan

No studies are planned.

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

Table 13-8 Major changes to the Risk Management Plan over time

RMP Version	RMP Date	Safety Concerns	Comment
5.1	18-Mar-2016	There are no new safety concerns in this version.	The already existing potential risk of serotonin syndrome is now delineated to also include serotonin syndrome following oral overdose of ondansetron in pediatric population.

RMP Version	RMP Date	Safety Concerns	Comment
5	11-Jun-2015	Added potential risks: Reduced clearance and prolonged half-life in patients with hepatic impairment Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility; Adverse events in breast-fed infants due to use of ondansetron during lactation Added missing information: Safety in pregnant women	Changes made in response to comments from Slovenia regulatory authority
4	27-Apr-2015	Added identified risks: Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride; Hypersensitivity; Toxic epidermal necrolysis Added potential risks: Serotonin syndrome; Adverse birth outcomes following use during pregnancy Added missing Information: Use during lactation	Complete RMP prepared in response to request from Slovenia
3	14-May-2013	QT interval prolongation and Torsade de Pointes	Revised version 2 in response to comments from MHRA
2	29-Apr-2013	QT interval prolongation and Torsade de Pointes	Revised version 1 in response to RMP Assessment Report
1	18-Feb-2013	QT interval prolongation and Torsade de Pointes	First RMP was a targeted RMP with one identified risk