VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Nausea and vomiting associated with chemotherapy and radiotheraphy:

One of the most distressing symptoms for patients undergoing both surgery and chemotherapy is nausea and vomiting. These symptoms have a significant impact on quality of life and can lead to malnutrition, inability to respond to treatment and an increased length of hospitalization. Emesis is more commonly associated with chemotherapeutic agents; however, radiation-induced nausea and vomiting (RINV) can affect a significant proportion of patients, depending on the treated area, dose fractionation, and volume of radiotherapy. The relative risk for developing nausea and vomiting with chemotherapy ranges from 30 to 90% and is dependent upon the chemotherapeutic agent used. Relative risk for nausea and vomiting with radiation therapy is approximately 40%.[2,3,4,5]

Post-operative nausea and vomiting

Postoperative nausea and vomiting (PONV) is a major source of patient dissatisfaction and is the leading cause of discharge delays and unanticipated postsurgical hospital admissions. In the absence of pharmacological treatment, the rate of PONV is approximately 30% in general population, and can be as high as 70% in patients at highest risk. Several risk factors as surgery type, female gender, non-smoker status, history of postoperative nausea and vomiting or motion sickness and post-operative opioid use have been acknowledged. Additionally, post-operative vomiting (POV) occurs twice as frequently in children as in adults, increasing until puberty and then decreasing to adult incidence rates. Gender differences are not seen before puberty. POV remains a main cause of morbidity in children because severe vomiting can be associated with dehydration, postoperative bleeding, pulmonary aspiration, and wound

dehiscence. The approach to the management of PONV and POV in children is similar to that in adults.[6,7]

VI.2.2 Summary of treatment benefits

The introduction of 5-HT_3 receptor antagonists into clinical use revolutionized the treatment of nausea and vomiting in cancer patients receiving chemo- or radiation therapy. At the time of ondansestron's release, dopamine D2 receptor antagonists, antihistamines, and anti-muscarinicswere the primary antiemetic pharmacotherapies. None of these three classes was as efficacious in decreasing emesis associated with cancer treatment as ondansetron proved to be. Similar to chemotherapy induced nausea and vomiting, this drug class appear to be most effective in the prophylaxis of nausea and vomiting and in the treatment of the early phase of PONV. Indeed, 5-HT_3 receptor antagonists, ondansetron, granlsetron and tropisetron are highly specific for the 5-HT_3 receptor and have a selectivity ratio of approximately 1000:1 compared with affinities for other receptors. Other 5-HT_3 receptor antagonists, largely those having a benzamide structure, are non-selective. These Include metoclopramide, renzapride and zacopride which stimulate gastric motility via activation of 5-HT4 receptors; metoclopramide is also a potent dopamine receptor antagonist. Selective 5-HT3 receptor antagonists are a major advance in the treatment of chemotherapy- and radiotherapy-induced emesis in cancer patients. They are also the antiemetic drugs of first choice for POV prophylaxis in children because as a group they have greater efficacy for preventing vomiting than nausea. The 5-HT_3 receptor antagonists can be effectively combined with dexamethasone with an increase in efficacy. As such 5-HT_3 receptor antagonists are recommended as the first-line treatment in chemotherapy induced nausea and vomiting in adults and children. They are also recommended for those patients undergoing surgery who are most at risk of postoperative nausea and vomiting. These drugs are most effective when given at the end of surgery. Additionally this drug class proved to be generally well tolerated with limited side effects. [2,4,7,8,9]

VI.2.3 Unknowns relating to treatments benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Reduction of lower bowel motility	Granisetron may reduce lower bowel motility. It is a well-known drug class effect.[1]	Patients with signs of sub-acute intestinal obstruction should be monitored following granisetron administration.
ECG changes (QT interval prolongation)	Clinical data have demonstrated ECG interval changes – among these QT-prolongations, which is associated with an increased risk of serious ventricular arrhythmias (for example *torsade de pointes*). This is a class effect of the 5-HT_3 receptor antagonists. These changes are also seen in children was well. These effects are dose related; and are considered to be clinically insignificant, as they are small in magnitude and are transient.[1,4,10] Regarding granisetron, while some studies found no significant adverse effects on pulse, blood pressure, or ECG measurements after a high dose intravenous granisetron, other studies reported ECG changes with granisetron. These studies concluded that intravenous granisetron causes minor transient changes in the ECG. [1]	Granisetron, as other drugs of the same class, should be used with caution in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with electrolyte abnormalities (problems with levels of salts, such as potassium, sodium or calcium).[1] Although no evidence of proarrythmia (a new or more frequent occurrence of pre-existing arrhythmias) has been noted following granisetron use, caution should be exercised when prescribing it to any patients with pre-existing arrhythmias or cardiac conduction disorders, as there is a potential that these changes may lead to clinical consequences.[1] Caution should be exercised when taking granisetron with other drugs known to cause QT prolongation.[10]

Risk	What is known	Preventability
Cross-reactivity between 5HT$_3$ antagonists	Cross-sensitivity between two 5-HT$_3$ antagonists, tropisetron and ondansetron has been reported in the literature. Regarding granisetron, to the date, cross-sensitivity is not reported in the literature. However, there is a theoretical risk of cross-sensitivity reactions with granisetron in patients who have previously reported hypersensitivity reactions to other 5-HT$_3$ antagonists.[1]	Health care professionals and patients who experienced previously hypersensitivity reactions with other 5-HT$_3$ antagonists should be aware of this theoretical risk.
Hypersensitivity reactions	A small number of idiosyncratic hypersensitivity reactions (adverse drug reactions that are not related to the known pharmacological properties of the drug occur in only a small percentage of the population and do not show any apparent dose–response relationship) to granisetron occurred during clinical testing.[11] Hypersensitivity reactions for granisetron and overall for 5-HT$_3$ receptor antagonists, have been reported very rarely. [1]	Granisetron must not be used in patients who are hypersensitive (allergic) to the active substance or to any of the excipients.[12]

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use during pregnancy	There are no studies in pregnant women Pregnancy Category B.

Risk	What is known (Including reason why it is considered a potential risk)
	Reproduction studies have been performed in pregnant rats and pregnant rabbits with intravenous dosages of granisetron revealed no evidence of impaired fertility or harm to the foetus due to granisetron. However there are no adequate and well-controlled studies in women; the data on the use of granisetron in pregnant women is very limited: there have been a small number of post-marketing case reports of patients becoming pregnant whilst receiving granisetron.[1,11] Granisetron should be avoided during pregnancy.

Important missing information

Risk	What is known
Interaction studies in anaesthetised patients	No specific interaction studies have been conducted in anaesthetised patients.
Use in children for prevention of post-operative nausea and vomiting	There is insufficient clinical evidence to recommend administration of the solution for injection to children in prevention and treatment of post-operative nausea and vomiting.
Use in breastfeeding women	It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with granisetron.[1]

VI.2.5 Summary of additional risk minimisation 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 minimising 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 minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6. Planned post authorisation development plan

Not applicable.

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

Version	Date	Safety Concerns	Comment
1.0	Not applicable.	N/A	First version of the RMP