VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Nausea and vomiting caused by chemotherapy

Two of the most common side effects with medicines given to kill cancer cells are nausea and vomiting. These side effects have a significant impact on quality of life and can interfere with the cancer treatment. The frequency of nausea and vomiting is related to the drug or combination of drugs being administered for cancer treatment. 99 % of the patients on Cisplatin cancer therapy experienced nausea if used without any nausea preventing drugs. Nausea and vomiting are mainly observed in child patients with cancer. Although both male and female are affected by vomiting and nausea with anti-cancer drugs however in some studies female patients experienced in more extent than male. Cancer drug-induced nausea

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and vomiting affects children of all ages; however, children younger than 6 years have been shown to have a lower occurrence than older children when receiving similar drugs.

Nausea and vomiting caused by radiotherapy

The patient receiving radiotherapy to kill cancer cells generally experienced nausea and vomiting. Around 50-80% of patients undergoing radiotherapy (RT) will experience nausea and/or vomiting. This may leads to number of medical complications like dehydration, electrolyte disturbance and even cause physical damage. The symptoms of nausea and vomiting depend upon radiotherapy-related factors like radiation dose & frequency, radiotherapy techniques and radiation site and patient-related factors (gender, general health of the patient, age, concurrent or recent chemotherapy, psychological state, disease stage).

Nausea and vomiting caused by migraine (headache)

Migraine is defined as recurrent episodes of headache.Migraine is a common disorder that affects approximately 10%–12% of the population of developed countries (18% of women and 6% of men), with similar prevalence rates in North America and Europe.The patients generally experienced nausea and/or vomiting during migraine attack.In addition to neurological changes, there can be hormonal changes that lead to nausea and vomiting with a migraine headache. Also, because migraines cause such intense pain, the vomiting and nausea is body's natural way of trying to manage the pain effectively.Nausea and vomiting during migraine attacks are common symptoms that affect at least 60% of patients suffering from migraines.

VI.2.2 Summary of treatment benefits

Metoclopramide belongs to class of anti-emetic medicines (medicines that prevent vomiting). It works on a part of brain that prevents from feeling sick (nausea) or being sick (vomiting).It works by helping to move the food in stomach through digestive system more quickly. Metoclopramide is often prescribed when the sickness is associated with a surgical operation, a migraine headache, or as a result of radiotherapy or medicines for cancer. Metoclopramide can be taken with oral painkillers in case of migraine to help painkillers work more effectively.Steroids, dexamethasone, metoclopramide, cannabinoids, benzodiazepines, 5-HT3

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receptor antagonists (ondansetron, granisetron, tropisetron) and a new group of antiemetics, the neurokinin1 receptor antagonists are used to prevent anticipatory, acute and delayed vomiting and nausea.

In one study, patient receiving ondansetron have no vomiting episode on day 1 compared to metoclopramide where as no emesis on days 2–5 for both ondansetron and metoclopramide groups. Metoclopramide was less likely to control acute vomiting but equivalent to ondansetron for controlling delayed chemotherapy induced nausea and vomiting.In patients with migraine headache-associated nausea, metoclopramide improves response to oral medicines used to treat nausea

VI.2.3 Unknowns relating to treatment benefits

None

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	**What is known**	**Preventability**
Disease pertaining to nervous system (Neurological disorders (including extrapyramidal symptoms, tardive dyskinesia & neuroleptic syndrome))	Patients may feel drowsy, dizzy or have uncontrollable twitching, jerking or writhing movements and unusual muscle tone causing distortion of the body after taking metoclopramide. This may affect your vision and also interfere with your ability to drive and use machines. Patients may experience uncontrollable movements (often involving head or neck). These may occur in children or young adults	Yes Do not take this medicine if you have disease pertaining to nervous system like involuntary muscle spasms (tardive dyskinesia), epilepsy, Parkinson disease. Talk to your doctor, pharmacist or nurse before taking this medicine if you have any neurological (brain)

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Risk	What is known	Preventability
	and particularly when high doses are used. Patients may experience very common (affect more than 1 in 10 people) side effects like feeling drowsy, common (affect up to 1 in 10 people) side effects like depression, uncontrollable movements such as tics, shaking, twisting movements or muscle contracture (stiffness, rigidity) and symptoms similar to Parkinson disease (rigidity, tremor), uncommon (affect up to 1 in 100 people) side effects like hallucination, decreased level of consciousness, rare (affect up to 1 in 1000 people) side effects like confusional state and convulsion (especially in patients with epilepsy) and not known (frequency cannot be estimated from available data) side effects like involuntary muscle spasm after prolonged use, especially in elderly patients, high fever, high blood pressure, convulsions, sweating and production of saliva. These may be signs of a condition called neuroleptic malignant syndrome.	problems. Stop the treatment and talk straight away to your doctor, pharmacist or nurse if you experience uncontrollable movements (often involving head or neck), high fever, high blood pressure, convulsions, sweating, production of saliva. Inform your doctor, pharmacist or nurse if you are taking, have recently taken or might take other medicines.

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Risk	What is known	Preventability
Risk of abnormal pigment le vel (methaemoglobinemia) due t o NADH cytochrome b5 r eductase deficiency	The pa tients m ay experience not known (frequency cannot be estimated from available da ta) s ide effect l ike abnormal bl ood pi gment level; w hich may ch ange t he col our of your skin.	Yes Do not take this medicine you have ev er ha d an abnormal bl ood pi gment levels (methaemoglobinemia) o r NADH c ytochrome-b5 deficiency. Doctor n eed to perform blood tests to check blood pigment le vels. In cases of a bnormal levels (methaemoglobinemia), the t reatment s hould b e immediately and permanently stopped. Inform your do ctor, pharmacist or nurse if you are t aking, have r ecently taken or m ight t ake ot her medicines.
Heart P roblems (Cardiac disorders) (including bradycardia, cardiac arrest and QT prolongation)	Metoclopramide can af fect on working of m edicine u sed t o t reat heart failure like digoxin. Patient m ay ex perience com mon (affect up t o 1 i n 10 p eople) s ide effects like blood pressure decreased (particularly with intravenous route), uncommon (affect up t o 1 i n 100	Yes Talk t o your doc tor, pharmacist or nur se before t aking t his medicine i f you ha ve history o f a bnormal heartbeat (QT i nterval prolongation) or any other

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Risk	What is known	Preventability
	people) side effect like slow heart beat (particularly with intravenous route) and not known (frequency cannot be estimated with available data) side effects like changes in heart beat, which may be shown in ECG test, cardiac arrest (particularly with injection route), shock (severe decreased of heart pressure) (particularly with injection route) and very high blood pressure.	heart problems. Talk to your doctor, pharmacist or nurse before taking this medicine if you are using other medicines known to affect the way your heart beats. Inform your doctor, pharmacist or nurse if you are taking, have recently taken or might take other medicines.

Important potential risks

Risk	What is known
Use in children ages less than 1 year and risk of neurological side effects	Do not give this medicine to a child less than 1 year of age. This medicine must not be used in children below 1 year of age because of the increased risk of the uncontrollable movements(extrapyramidal disorders). Patients may experience uncontrollable movements (often involving head or neck). These may occur in children or young adults and particularly when high doses are used. These signs usually occur at the beginning of treatment and may even occur after one single administration

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Risk	What is known
Use of metoclopramide during pregnancyand risk of neurological adverse reactions in neonates	If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before being given this medicine. This medicine may be taken during pregnancy. Due to drug properties, in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in newborn cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken. Your doctor will decide whether or not you should be given this medicine.
Use of metoclopramide for more than 5 days	The maximum recommended treatment duration is 5 days. Patient should not take this medicine for more than 5 days to prevent delayed nausea and vomiting that may occur after chemotherapy

Missing information

Risk	What is known
Nil	-

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.

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VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
2.0	29 July 2015	Following important potential risk has been added - long term use (> 5 days) Following important identified risks have been removed - Acute h ypertension i n pa tients with pheochromocytoma -Drug i nteraction w ith l evodopa or dopaminergic agonists	RMP has been update as per Type I I variation Preliminary Variation Assessment R eport of Metoclopramide hydrochloride Accord 10 mg (NL/H/2418/001/II/012), dated 08 July 2015.

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