9.2 Part VI.2 Elements for a Public Summary

9.2.1 Part VI.2.1 Overview of disease epidemiology

Cancer is one of the leading causes of death worldwide with lung cancer (1.8 million; 13.0%), breast cancer (1.7 million; 11.9%), and colorectal cancer (1.4 million cases; 9.7%) being the most commonly diagnosed cancers. The most common death causing cancers were cancers of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%). Breast cancer is also the most common cause of cancer death among women (522 000 deaths in 2012) and the most frequently diagnosed cancer among women. Cervical cancer is the fourth common cancer affecting women worldwide [WHO, 2013]. There were an estimated 3.45 million new cases of cancer and 1.75 million deaths from cancer in Europe in 2012 [Ferlay, 2013]. Cancer mortality is higher among men than women. In 2014, an estimated 15,780 children and adolescents ages 0 to 19 were diagnosed with cancer and 1,960 died of the disease [NIH, 2016].

9.2.2 Part VI.2.2 Summary of treatment benefits

Calcium folinate is the calcium salt of a vitamin called folinic acid, used to treat anemia (decrease in the amount of red blood cells) caused by a deficiency of folic acid in the body (megaloblastic anemia). In cancer treatment with the chemotherapy (treatment with chemicals) medicine MTX, calcium folinate is given for 'folinic acid rescue therapy' that helps healthy cells to recover from the effects of the MTX. [Netdoctor, 2013]. It also provides a protective effect against MTX in patients suffering with rheumatoid arthritis (pain and inflammation of small joints) and shows a significant reduction in the occurrence of gastrointestinal side effects, liver dysfunctions and also a significant reduction in the discontinuation of MTX treatment [Shea, 2013].

Calcium folinate is used along with 5-fluorouracil (an anti-cancer drug) to enhance its anti-cancer activity [SmPC]. Safety and tolerance of weekly paclitaxel plus 5-fluorouracil/ calcium folinate is used as a first line therapy in patients with untreated gastric cancer [Deng, 2013]. FOLFIRI (combination of folinic acid, fluorouracil and irinotecan) chemotherapy has a modest efficacy with acceptable toxicities in patients with advanced gastric cancer as a second line treatment [Kwon, 2015].

9.2.3 Part VI.2.3 Unknowns relating to treatment benefits

It is not known whether calcium folinate is excreted into human breast milk. Calcium folinate can be used during breast feeding when considered necessary according to the therapeutic indications.

9.2.4 VI.2.4 Summary of safety concerns

Table 9-4 Important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	Hypersensitivity to calcium folinate or to any of the excipients is observed very rarely (< 1/10000) in patients treated with calcium folinate.	Patient is advised not to take calcium folinate if allergic to calcium folinate or any of the other ingredients of this medicine.
	Signs and symptoms of allergic reactions include sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and fainting.	Doctor should be informed immediately if the patient experiences any of the side effects, and medical attention is required.

Risk	What is known	Preventability
Interaction with the anti-cancer drugs that block the action of folic acid (Vitamin B9) (Interaction with folic acid antagonists)	When calcium folinate is given along with folic acid antagonist (e.g. co trimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely lost.	Doctor or pharmacist should be informed if the patient is taking, have recently taken or might take folic acid antagonist (co trimoxazole, and pyrimethamine) as they should not be used in combination with calcium folinate. Calcium folinate should not be given along with MTX during pregnancy or breast-feeding as it might harm the baby.
Increased risk of toxicity of the 5-fluorouracil, an anti-cancer drug particularly in elderly or severely ill patients (Enhanced risk of toxicity of 5-fluorouracil, particularly in elderly or debilitated patients)	Frequency and severity of adverse reactions associated to 5-fluorouracil may increase. Calcium folinate may enhance the toxicity of 5-fluorouracil, particularly in elderly or severely ill patients. The most common symptoms are leukopenia (reduction in the number of white cells in the blood), mucositis (pain and inflammation of the body's mucous membrane), stomatitis (inflammation of the mucous membrane of the mouth) and/or diarrhoea which may be dose limiting	Doctor or pharmacist should be informed if the patient is taking, have recently taken or might take any other medicines, including 5-fluorouracil. Combined treatment of 5-fluorouracil and calcium folinate should neither be initiated nor maintained in patients with symptoms of gastrointestinal toxicity, regardless of the severity, until all of these symptoms have completely disappeared. Calcium folinate should not be given along with 5-Fluorouracil during pregnancy or breast-feeding as it might harm the baby.
Impairment of anti-cancer activity of MTX in combination with high dose of calcium folinate (Impairment of antitumor activity of MTX with high dose of Calcium Folinate)	Excessive amounts of calcium folinate may result in a reduced efficacy of folic acid antagonists such as methotrexate (anti-cancer drug).	Excessive calcium folinate doses must be avoided since this might impair the anti-cancer activity of MTX, especially in tumors of brain where calcium folinate accumulates after repeated courses.
Interaction with drugs such as phenobarbital, phenytoin, primidone, and succinimide that are used in treating fits resulting in increased frequency of seizures in patients with history of	Calcium folinate may diminish the effect of the anti-epileptic substances (phenobarbital, primidone and phenytoin, succinimides), and may increase the frequency of seizures due to an increased metabolism of those	Doctor or pharmacist should be informed if the patient is taking, have recently taken and might take any other medicines, for the treatment of fits.

Risk	What is known	Preventability
epilepsy (Drug interaction with phenobarbital, phenytoin, primidone, and succinimides resulting in increased frequency of seizures in epileptic patients)	substances. Seizures in epileptic patients treated with phenobarbital, phenytoin, primidone, and succinimides have been reported rarely (1 in 1000 people).	Before taking calcium folinate, the doctor should be informed regarding any history of epilepsy. Monitoring of blood levels and, if necessary dose adjustment of the anti-epileptic drug, during and after calcium folinate administration is recommended.
Masking signs and symptoms of pernicious anemia (decrease in red blood cells count due to a lack of vitamin B12) due to deficiency of vitamin b 12 deficiency (Masking of Pernicious anemia or other anemias due to vitamin B12 deficiency)	Calcium folinate treatment may mask pernicious anemia and other anemias (decrease in the count of red blood cells) resulting from vitamin B12 deficiency.	Patient is advised not to take calcium folinate if have a decrease in the count of red blood cells (anaemia).

Table 9-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Risk of death by administration of drug directly into the spine or brain (Risk of death from intrathecal route of administration)	Calcium folinate should only be given by intramuscular or IV route of injection and must not be administered directly into the spine or brain (intrathecally). Death has been reported when folinic acid has been administered intrathecally, following intrathecal overdose of MTX

Table 9-5 Missing information

Risk	What is known
Use in pregnant or breast-feeding women	There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. There is no indication that folinic acid induces harmful effects if administered during pregnancy. Calcium folinate should not be given along with 5-Fluorouracil and MTX during pregnancy or breast-feeding as it might harm the baby. Calcium folinate should only be given together with MTX during pregnancy or breast-feeding if the doctors think it is necessary.

Risk	What is known
	It is not known whether calcium folinate is excreted into human breast milk. Calcium folinate can be used during breast feeding when considered necessary according to the therapeutic indications.”

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

All medicines have a 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.

9.2.6 Part VI.2.6 Planned post authorization development plan

N/A

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

Not applicable, this is the first version.