## VI.2 Elements for a Public Summary

### VI.2.1 Overview of Disease Epidemiology

***Toxicity of Folic acid antagonists***

Despite having a low frequency of major toxicity, low dose Methotrexate (MTX, folic acid antagonist) use is limited by side effects in certain patients resulting in interruptions or discontinuation of therapy. The major limiting factor for MTX use is its toxicity. 30-90% of patients develop side effects including nausea, loss of appetite, stomatitis, diarrhoea gastrointestinal intolerance, gastroduodenal atrophy, headache, fatigue, rash, malaise, alopecia,

hematologic abnormalities (anaemia, cytopenias, macrocytosis), hepatotoxicity, flu-like syndrome, tremors, visual loss/toxic optic neuropathy, and pulmonary toxicity. Liver toxicity may be the most common limitation of MTX treatment in psoriasis patients, and although the exact mechanism is unclear, MTX-induced hepatotoxicty is believed to be caused by MTX accumulation in hepatocytes. Since high cumulative exposure to MTX can predispose to liver fibrosis, periodic liver biopsies should be considered though this is physician dependent. The side effects mentioned above are related to folate deficiency.

Most cases of catastrophic pancytopenia following MTX treatment occur in the context of folate deficiency. Before initiation of MTX, some recommend patients be screened for low plasma folate levels because folate-depleted patients started on MTX therapy are predisposed to MTX toxicity. This has been demonstrated in studies exploring MTX treatment for RA as well as at chemotherapy doses for head and neck tumors. Thus, marginal folate levels are a contraindication for MTX therapy in patients with psoriasis, asthma, and an array of other conditions.

Even patients with sufficient folate levels may become folate depleted as long term MTX therapy impairs folate status. Plasma folate levels become depleted in patients with RA or psoriasis during long-term low dose MTX therapy. Even untreated psoriasis patients may show signs of folate deficiency. Depletion of folate stores has been associated with severe psoriasis and may be caused by reduced intestinal absorption and/or increased utilization of folate by the skin as a result of a rapid rate epidermal cell turnover. Loss of folate in desquamated cells is very high which may account for the decreased folate levels. In rheumatoid arthritis and other diseases, low levels of plasma folate in association with low-dose MTX is likely secondary to decreasing intestinal absorption of this vitamin.

Calcium Folinate is a fully-reduced stable folate coenzyme 3 and is used in high doses to reverse serious events of acute MTX toxicity. The ability to reverse these episodes led to the evaluation of folate supplementation in patients undergoing low-dose MTX therapy. Calcium Folinate is essential for the growth and metabolism of cells, and by operating as a carbon donor, this B vitamin promotes thymidylate and purine synthesis as well as remethylation of homocysteine to methionine. Calcium Folinate has been used to replenish folate deficiency in patients and counter toxicity associated with MTX treatment. [1] (Annex 12)

### VI.2.2 Summary of Treatment Benefits

Over 50 years, experience has been gained with the clinical use and safety of Calcium Folinate.

Calcium Folinate use with Methotrexate therapy and in combination with 5-Fluorouracil (especially in colorectal cancer) is considered well established even if various posologies exist, especially for the latter. Calcium Folinate is also recognized as antidote for other folic acid antagonists Trimetrexate, Trimethoprime and Pyrimethamine. Finally, IV Calcium Folinate can be administered for the prevention and treatment of folate deficiency when it cannot be prevented or corrected by the administration of Folic acid by the oral route. [2] (Annex 12)

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### VI.2.3 Unknowns relating to treatment benefits

Clinical studies with Calcium Folinate in combination with 5-Fluorouracil have not been performed in children. The safety and effectiveness of Calcium Folinate with 5-Fluorouracil in children has not been established and therefore this combination therapy cannot be recommended for use in this age group.

### VI.2.4 Summary of safety concerns

| Safety Concern | What is known | Preventability |
|---|---|---|
| **Important Identified Risks** | | |
| Hypersensitivity | Allergic hypersensitivity to Calcium Folinate can occur in some patients. | Yes by monitoring of early symptoms. Tell doctor immediately if you notice signs of allergic reaction or hypersensitivity.<br>Do not take Calcium Folinate if you are allergic to Calcium Folinate or any of the other ingredients of this medicine. |
| Masking of Pernicious anaemia or other anaemias due to vitamin B12 deficiency | Calcium Folinate treatment may mask pernicious anaemia and other megaloblastic anaemias resulting from vitamin B12 deficiency. Therefore, Calcium Folinate should not be used in such cases. | Consult your doctor about any such treatment before administration of Calcium Folinate. |
| Risk of death from intrathecal route of administration | Calcium Folinate is administered parenterally as intramuscular injection or intravenous injection or infusion. Death has been reported is cases of Calcium Folinate administered intrathecally, following intrathecal overdose of Methotrexate. | Calcium folinate should only be given by intramuscular injection or intravenous injection or infusion and must not be administered intrathecally. |

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| Safety Concern | What is known | Preventability |
|---|---|---|
| Treatment for Macrocytosis caused by cytotoxic medicinal products | Calcium Folinate is not recommended for treatment of macrocytosis caused by cytotoxic medicinal products like Hydroxycarbamide, Cytarabine, Mecaptopurine and Thioguanine. | Consult your doctor about any such treatment before administration of Calcium Folinate. |
| Low levels of Calcium | Calcium levels should be monitored in patients receiving combined 5-Fluorouracil/Calcium Folinate treatment and Calcium supplementation should be provided if calcium levels are low. | Yes by monitoring of early detection symptoms. Consult your doctor about any such treatment before administration of Calcium Folinate.<br>Your doctor will carry out tests to monitor the levels of Calcium in body and may provide Calcium supplementation in case of low levels. |
| Simultaneous use of Calcium Folinate with one of the following medicines results in reduction of their therapeutic effect:<br>- Phenobarbital, Phenytoine, Primidone, and Succinimides | Decrease in plasma concentration and therapeutic effect of anti-epileptic drugs leading to increase in frequency of seizures. | Consult your doctor about any such treatment before administration of Calcium Folinate.<br>Monitoring of plasma concentrations and dose modification of anti-epileptic drugs is recommended during Calcium Folinate administration or after its discontinuation. |

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| Safety Concern | What is known | Preventability |
|---|---|---|
| Simultaneous use of Calcium Folinate with 5-Fluorouracil results in increased efficacy and toxicity of the latter | The toxicity risk of 5-Fluorouracil is increased by Calcium Folinate, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. | Yes by monitoring of early detection symptoms.<br>The combined 5-Fluorouracil/ Calcium Folinate treatment should neither be initiated nor maintained especially in elderly or debilitated patients with symptoms of gastrointestinal toxicity. The patients presenting with diarrhoea must be carefully monitored until disappearance of symptoms, since rapid clinical deterioration can result to death.<br>Your doctor may recommend modification of 5-Fluorouracil dosage and the treatment-free interval may be opted depending on patient condition, clinical response and dose limiting toxicity. A reduction of Calcium Folinate dosage is not required. |
| Simultaneous use of Calcium Folinate with one of the following medicines results in reduction of their efficacy:<br>- Cotrimoxazole, Pyrimethamine | Chemotherapeutic effect of Folic Acid antagonists (e.g. cotrimoxazole, pyrimethamine) may either get reduced or completely neutralized. | Consult your doctor about any such treatment before administration of Calcium Folinate. |

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**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Impairment of antitumour activity of Methotrexate with high dose of Calcium Folinate | Excessive Calcium Folinate doses must be avoided since this might impair the antitumour activity of Methotrexate, especially in CNS tumours where Calcium Folinate accumulates after repeated courses. |

**Missing information**

| Risk | What is known |
|---|---|
| Limited information on use in breast-feeding women | 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. |
| Limited information on use in pregnant women | Clinical studies with Calcium Folinate have not been performed in pregnant women. The safety and effectiveness of Calcium Folinate in pregnant women has not been established and therefore the product cannot be recommended for use in these patients. |

### VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics and the Package Leaflet for Calcium folinate 10 mg/ml solution for injection or infusion contain information about routine 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

Not applicable.