CITOFOLIN (folinic acid / (di)sodium folinate / calcium folinate)

Recommendations:

ANNEX I (Updated 15/10/2015)

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION (02/09/2015)

Folinic acid (FA), generally administered as calcium or sodium folinate, is the formyl derivative of tetrahydrofolic acid (THF). Levofolinic acid and its salts are the 2S- form of the molecule. They are the only molecules that are biologically active; for this reason we grouped for this procedure the active substances folinic acid / (di)sodium folinate / calcium folinate / calcium levofolinate.
The safety information resulted from the Referral procedure on Calciumfolinat, Lederfolin, Ledervorin Calcium, Leucovorin, (procedure EMEA/H/A-30/451, Decision (2003)2244 of 30/06/2003) mostly remain appropriate to cover the safety profile of the injectable pharmaceutical formulations and represent the basic core information.
Updates of the PI are deemed necessary, in order to include the evidence of anaphylactic reactions, hyperammonaemia, palmar-plantar erythrodysaesthesia, bone marrow failure, general disorders and administration site conditions.
The reference text is the following, and should be implemented according to the authorized indications of the respective medicinal products, for injectable formulations of folinic acid / (di)sodium folinate / calcium folinate / calcium levofolinate-containing products; text in [] applies onlt to MPs authorized for use in combination with 5-FU.

Summary of Product Characteristics

4.3 Contraindications

- Known hypersensitivity to calcium folinate, or to any of the excipients.
- Pernicious anaemia or other anaemias due to vitamin B12 deficiency.

Regarding the use of calcium folinate with methotrexate [or 5-fluorouracil] during pregnancy and lactation, see section 4.6, “Pregnancy and Lactation” and the summaries of product characteristics for methotrexate- [and 5-fluorouracil] containing medicinal products”.

4.4 Special warnings and special precautions for use

<active substance> should only be given by intramuscular or intravenous injection and must not be administered intrathecally. When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate death has been reported.

General

<active substance> should be used with methotrexate [or 5-fluorouracil] only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.
<active substance> treatment may mask pernicious anaemia and other anaemias resulting from vitamin B12 deficiency.
Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mecaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.
In epileptic patients treated with phenobarbital, phenytoine, primidone, and succinimides there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during <active substance> administration and after discontinuation is recommended (see also section 4.5 Interactions).

[<active substance>/5-fluorouracil

<active substance> may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When <active substance> and 5-fluorouracil are used in combination, the 5- fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.
Combined 5-fluorouracil/<active substance> treatment 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.

Because diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur.If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.
In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil.
<active substance> must not be mixed with 5-fluorouracil in the same IV injection or infusion.
Calcium levels should be monitored in patients receiving combined 5-fluorouracil/<active substance> treatment and calcium supplementation should be provided if calcium levels are low.]

<active substance>/methotrexate
For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.
<active substance> has no effect on non-haematological toxicities of methotrexate such as the nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney. Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and all toxicities associated with methotrexate (please refer to the SPC for methotrexate). The presence of preexisting- or methotrexate-induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of <active substance>.
Excessive <active substance> doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where <active substance> accumulates after repeated courses.
Resistance to methotrexate as a result of decreased membrane transport implies also resistance to folinic acid rescue as both medicinal products share the same transport system.
An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between methotrexate administration and <active substance> rescue increases, <active substance> effectiveness in counteracting toxicity decreases.
The possibility that the patient is taking other medications that interact with methotrexate (eg, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

4.5 Interaction with other medicinal products and other forms of interaction
When <active substance> is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.
<active substance> may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoine and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also sections 4.4 and 4.8).
Concomitant administration of <active substance> with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil [(see sections 4.2, 4.4 and 4.8)].

4.6 Pregnancy and lactation
Pregnancy
There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with <active substance> have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of <active substance> to diminish toxicity or counteract the effects.
[5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of <active substance> with 5-fluorouracil.]
Please refer also to the summaries of product characteristics for methotrexate-, other folate antagonists [and 5-fluorouracil-] containing medicinal products.
Lactation
It is not known whether <active substance> is excreted into human breast milk. <active substance> can be used during breast feeding when considered necessary according to the therapeutic indications.

4.7 Effects on ability to drive and use machines
There is no evidence that <active substance> has an effect on the ability to drive or use machines.

4.8 Undesirable effects
[All therapeutic indications:]
Immune system disorders
Very rare (<0.01%): allergic reactions, including anaphylactoid / anaphylactic reactions, and urticaria.
Psychiatric disorders
Rare (0.01-0.1%): insomnia, agitation and depression after high doses.
Gastrointestinal disorders
Rare (0.01-0.1%): gastrointestinal disorders after high doses.
Neurological disorders
Rare (0.01-0.1%): increase in the frequency of attacks in epileptics (see also section 4.5 Interactions).
General disorders and administration site conditions
Uncommon (0.1-1%): fever has been observed after administration of <active substance> as solution for injection.

[Combination therapy with 5-fluorouracil:
Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities.

Metabolism and Nutritional Disorder ~~Hepatobiliary disorders~~:
Not known: Hyperammonaemia
Blood and lymphatic system disorders:
Very common~~Not known~~: bone marrow failure, including fatal cases
General disorders and administration site conditions
Very common: Mucositis, including stomatitis and chelitis. Fatalities have occurred as a result of mucositis
Skin and subcutaneous tissue disorders:
Common~~Not known~~: Palmar-Plantar Erythrodysaesthesia

Monthly regimen:
Gastrointestinal disorders
Very common (>10%): vomiting and nausea

No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity).

Weekly regimen:
Gastrointestinal disorders
Very common (>10%): diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.]

4.9 Overdose
There have been no reported sequelae in patients who have received significantly more calcium folinate than the recommended dosage. However, excessive amounts of <active substance> may nullify the chemotherapeutic effect of folic acid antagonists.
[Should overdosage of the combination of 5-fluorouracil and <active substance> occur, the overdosage instructions for 5-FU should be followed.]

Package Leaflet

2. BEFORE YOU USE <ACTIVE SUBSTANCE> INJECTION
<Active substance> Injection must not be injected intrathecally (into the spine).
Do not use <Active substance> Injection
- if you have shown signs of hypersensitivity (severe allergy) to <active substance> in the past
- if you have a type of anaemia caused by too little vitamin B12

Take special care with <active substance> Injection
If you are to receive <active substance> and fluorouracil treatment at the same time take special care if:

- you have had radiotherapy
- you have stomach or bowel trouble

Tell your doctor if the above applies to you before this medicine is used.
Special care is also needed if you are elderly and you are to receive <active substance> and fluorouracil treatment at the same time.

Taking/using other medicines
Special care is needed if you are taking/using other medicines as some could interact with <active substance> Injection, for example:

- folic acid antagonists (e.g. cotrimoxazole, pyrimethamine) - the effectiveness of these medicines will be reduced by <active substance>
- fluorouracil (anti-cancer medicine) – the effectiveness and side effects of this medicine will be increased by <active substance>
- medicines used to treat epilepsy (phenobarbitone, phenytoin, primidone or succinimides) – the effectiveness of these medicines may be reduced by <active substance>. Your doctor may check blood levels of these medicines and change your dose to prevent increased convulsions (fits)

Pregnancy and breast-feeding
Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding.
It is unlikely that your doctor will ask you to take/use a folic acid antagonist or fluorouracil whilst you are pregnant or breast-feeding. However, if you have taken/used a folic acid antagonist whilst pregnant or breast-feeding, this medicine (<active substance>) may be used to reduce its side effects.

3. HOW TO USE CALCIUM FOLINATE INJECTION

[…]

If you take more <active substance> than you should
Excessive amounts of <active substance> may nullify the chemotherapeutic effect of folic acid antagonists.
Should overdosage of the combination of 5-fluorouracil and <active substance> occur, the overdosage instructions for 5-FU should be followed.

4. POSSIBLE SIDE EFFECTS

Very rare: may affect up to 1 in 10,000 people

- severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint This is a serious side effect. You may need urgent medical attention.

Uncommon: may affect up to 1 in 100 people

- fever

Rare: may affect up to 1 in 1,000 people:

- an increase in convulsions (fits) in patients with epilepsy
- depression
- agitation
- problems with the digestive system
- difficulty sleeping (insomnia)

If you receive <active substance> in combination with an anticancer medicine containing fluoropyrimidines, it is more likely that you experience the following side effects of this other medicine:

Very common: may affect more than 1 in 10 people

- nausea

- vomiting
- severe diarrhoea
- drying out which may be due to ~~diarrhoea~~diarrhea
- inflammation of the lining of the intestine and mouth (life-threatening conditions have occurred)
- reduction in the number of blood cells (including life-threatening conditions)

Common

- redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot syndrome)

Not known: frequency cannot be estimated from the available data

- elevated ammonia level in the blood
- ~~reduction in the number of blood cells (including life-threatening conditions)~~
- ~~redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot syndrome)~~