1 NAME OF THE MEDICINAL PRODUCT

Isovorin, 10 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levofolinic acid 10 mg/ml as calcium levofolinate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear yellowish solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

High dose treatment with methotrexate. Advanced colorectal cancer during treatment with 5-fluorouracil.

4.2 Posology and method of administration

Methotrexate treatment:
The dosage varies with the given dose of methotrexate. During high dose treatment with methotrexate (>l g to adults) information concerning the Isovorin dose should be obtained from available literature. The following general guidelines can be given: the administration of Isovorin should be started 24 hours after already begun therapy with methotrexate. 5 mg Isovorin per m^2 body surface (about 7.5 mg) given every 6 hours 10 times is usually sufficient to reverse the toxic effects of methotrexate. Serum levels of methotrexate should be monitored if possible, especially when slow elimination of methotrexate is suspected. If the serum level of methotrexate exceeds $2x10^{-5}$M 24 hours after administration or if it exceeds $2xl0^{-6}$ M 48 hours after administration, the dosage of Isovorin should be increased or be given as an intravenous infusion. If the methotrexate level exceeds $2x10^{-7}$M 72 hours after administration further four doses of Isovorin (7.5 mg) should be given every 6 hours. Treatment with Isovorin should continue until the methotrexate level is less than $5xl0^{-8}$ M.
In the case of intravenous administration, no more than 160 mg of Isovorin should be injected per minute due to the calcium content of the solution.

Methotrexate overdosage:
The dose should be at least half of the given amount of methotrexate and be given within one hour.

Treatment with Isovorin / 5-fluorouracil:
Isovorin should be given as a dose of 100 mg per m^2 body surface as a slow intravenous injection during at least 3 minutes followed by 5-fluorouracil 370 mg per m^2 body surface given as an intravenous injection. The treatment should be repeated daily for 5 days. The five days treatment may be given with an interval of 4 weeks (28 days) in 2 turns and thereafter with intervals of 4-5 weeks (28-35 days) if the patient has recovered from the toxic effects of previous treatment. The dose of 5-fluorouracil should be adjusted according to the patient's response to the previous treatment. The daily dose of 5-fluorouracil should be reduced with 20% in patients with moderate haematological and gastrointestinal toxic effects during previous treatment and with 30% in patients with severe toxic effects. Patients who have not experienced any toxic effects in previous treatment may receive a 10% increase of the 5-fluorouracil dose. The Isovorin dose need not be changed.

Monitoring advice
Blood status should be monitored in patients treated with Isovorin/ 5-fluorouracil. Electrolytes and liver function tests: Prior to each treatment for first three courses; prior to every other course thereafter. Methotrexate/Isovorin therapy: Serum creatinine levels and serum methotrexate levels are recommended to be determined at least daily. Urine pH: In case of methotrexate overdose or delayed secretion, monitor as appropriate, to ensure maintenance of pH $\geq$7.0. Patients with diarrhoea must be followed especially carefully until the diarrhoea has ceased. Elderly and weak patients run a higher risk at developing gastrointestinal toxicity.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pernicious anaemia or other megaloblastic anaemias due to vitamin B_{12} deficiency.

4.4 Special warnings and special precautions for use

Isovorin 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.

Isovorin treatment may mask pernicious anaemia and megaloblastic anaemias caused by deficiency of vitamin B_{12}. Use of levoleucovorin calcium in combination with antineoplastic agents should be directly supervised by a clinician experienced in the use of cancer chemotherapy. Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoin, 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 Isovorin administration and after discontinuation is recommended (see also section 4.5 Interactions).

Isovorin/methotrexate
For specific details on reduction of methotrexate toxicity refer to the SPC for methotrexate.
An accidental overdose with a folate antagonist, such as methotrexate, should be treated quickly as a medical emergency. As the time interval between methotrexate administration and Isovorin rescue increases, Isovorin effectiveness in counteracting toxicity decreases.

Isovorin 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 pre-existing 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 Isovorin.

The possibility that the patient is taking other medications that interact with methotrexate (e.g., medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.
Excessive Isovorin doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where Isovorin accumulates after repeated courses.
Delayed methotrexate excretion caused by third space fluid accumulation, renal insufficiency or inadequate hydration may require levoleucovorin calcium be administered in higher doses or for longer periods.

Seizures and syncope have been reported in oncology patients receiving leucovorin calcium, most typically patients with CNS metastases treated concomitantly with fluropyrimidine.
Leucovorin calcium reduces the effect of folic acid antagonists when administered concomitantly.

Isovorin/5-fluorouracil
Isovorin may enhance the toxicity profile of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopoenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When Isovorin 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/Isovorin treatment should neither be initiated nor maintained in patients with symptoms of GI 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. The elderly and patients with a low physical performance due to their illness are especially 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.

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/Isovorin treatment and calcium supplementation should be provided if calcium levels are low.

4.5 Interaction with other medicinal products and other forms of interaction

Isovorin increases the toxic effects of 5-fluorouracil.

When Isovorin 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.

Isovorin may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures. High-dose leucovorin calcium may reduce the efficacy of intrathecally administered methotrexate.

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 Isovorin 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 Isovorin to diminish toxicity or counteract the effects.

Lactation:
It is not known whether Isovorin is excreted in human milk. Isovorin can be used during breast feeding when considered necessary according to the therapeutic indications.
Isovorin in combination with 5-fluorouracil should only be used in woman who are breast-feeding if the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Isovorin

System Organ Class	**Uncommon (<1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Frequency not known** (the undesirable effects have been reported but cannot be estimated from the available data)
Immune system disorders			Allergic reactions, including anaphylactoid /anaphylactic reactions, and urticaria	
Psychiatric disorders		Insomnia, agitation and depression after high doses.		
Nervous system disorders		Increase in the frequency of attacks in epileptics (see also section 4.5 Interactions),		
Gastrointestinal disorders		Gastrointestinal disorders after high doses.		
Skin and subcutaneous tissue disorders				Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)*
General disorders and administration site conditions	Fever has been observed after administration of levoleucovorin as solution for injection.			

*Some fatal, have been reported in patients receiving Isovorin in combination with other agents known to be associated with these disorders. A contributory role of Isovorin in these occurrences of SJS/TEN cannot be excluded.

Isovorin in combination with 5-fluorouracil

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities. Additional undesirable effects when used in combination with 5-flourouracil.

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Frequency not known (the undesirable effects have been reported but cannot be estimated from the available data)
Blood and lymphatic system disorders			Bone marrow failure, including fatal cases
Metabolism and nutritional disorders			Hyperammonaemia
Skin and subcutaneous tissue disorders		Palmar-Plantar Erythrodysaesthesia	
General disorders and administrative site conditions	Mucositis, including stomatitis and chelitis. Fatalities have occurred as a result of mucositis.		

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhea) and myelosuppression.

In patients with diarrhea, rapid clinical deterioration leading to death can occur.

Monthly regimen:

System Organ Class	Very Common (≥1/10)
Gastrointestinal disorders	Nausea and vomiting, diarrhea

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

Weekly regimen:

System Organ Class	Very Common (≥1/10)
Gastrointestinal disorders	Diarrhea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more Isovorin than the recommended dosage. However, excessive amounts of leucovorin calcium may nullify the chemotherapeutic effect of folic acid antagonists.

Should overdosage of the combination of 5-fluorouracil and Isovorin occur, the overdosage instructions for 5-FU should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment ATC code: V03AF04

Folinic acid is a formyl derivative of folic acid and consists of equal parts of the two isomers l-leucovorin and d-leucovorin. L-leucovorin is the active isomer. It is used in the same indications as d,l-leucovorin but only half of the amount is needed.

5.2 Pharmacokinetic properties

The degree of protein binding of l-leucovorin in plasma is about 27 %. The volume of distribution is 17.5±1.1 litres. Only about 20 % is excreted unchanged in the urine because l-leucovorin is metabolized to a great extent to the active metabolite 5- methyltetrahydrofolinic acid. Clearance for l-leucovorin is 205 ml/min. The half life for l-leucovorin and the active metabolite after intravenous administration is approx. 0.5 hours and 6.5 hours respectively.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Hydroxide or Hydrochloric Acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

Incompatibilities have been reported between injectable forms of calcium levofolinate and injectable forms of fluorouracil and methotrexate.

Fluorouracil
Calcium levofolinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/mL with calcium levofolinate 20 mg/mL, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different amounts and stored at 4°C, 23°C, or 32°C in polyvinyl chloride containers.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

6.5 Nature and content of container

Injection vials 2.5 ml, 5 ml and 17.5 ml

Vial: 2.5 ml
Type I amber glass, grey bromobutyl rubber stopper, and plastic/aluminium flip-off violet cap.

Vial: 5 ml

Type I amber glass, grey bromobutyl rubber stopper, and plastic/aluminium flip-off white cap.

Vial: 17.5 ml
Type I amber glass, grey bromobutyl rubber stopper, and plastic/aluminium flip-off yellow cap.

6.6 Special precautions for disposal and other handling

Prior to administration, Isovorin should be inspected visually. The solution for injection should be a clear and yellowish solution. If cloudy in appearance or if particles are observed, the solution should be discarded. Isovorin solution for injection is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

[To be completed nationally] 2016-06-08