# ANNEX I

# LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

| Member State | Marketing Authorisation Holder | Name | Strength | Pharmaceutical Form | Route of administration | Packaging | Content/ concentration | Package-size |
|---|---|---|---|---|---|---|---|---|
| Austria | Wyeth Lederle Pharma GmbH<br>Storchengasse 1<br>A-1150 Wien<br>Austria | Leucovorin | 3 mg/1 ml | Solution for injection | IV or IM | Ampoule | 3 mg/ml | 10 |
| | | Leucovorin | 10 mg/1 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1 |
| | | Leucovorin | 30 mg/3 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1 |
| | | Leucovorin | 50 mg/5 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 25 |
| | | Leucovorin | 100 mg/10 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 25 |
| | | Leucovorin | 200 mg/20 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 25 |
| | | Leucovorin | 300 mg/30 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 25 |
| Belgium | AHP Pharma S.A.,<br>Rue du Bosquet 15,<br>1348 Louvain la Neuve<br>Belgium | Ledervorin Calcium | 3 mg/1 ml | Solution for injection | IV or IM | Ampoule | 3 mg/ml | 6 |
| | | Ledervorin Calcium | 50 mg/5 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 10 |
| | | Ledervorin Calcium | 100 mg/10 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1, 10 |
| | | Ledervorin Calcium | 300 mg/30 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Ledervorin Calcium | 500 mg/50 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Germany | Wyeth Pharma GmbH<br>Wienburgstr. 207, D<br>48159 Munster | Leucovorin | 30 mg | Powder for solution for injection | IV or IM | Vial | 30 mg | 1, 5, 10 |
| | | Leucovorin | 3 mg/1 ml | Solution for injection | IV, IM | Ampoule | 3 mg/ml | 1, 5, 10, 50, 100 |
| | | Calciumfolinat | 10 mg/1 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Calciumfolinat | 100 mg/10 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Calciumfolinat | 300 mg/30 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1 |
| | | Calciumfolinat | 300 mg/30 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Calciumfolinat | 500 mg/50 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Calciumfolinat | 900 mg/90 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Calciumfolinat | 1000 mg/100 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Leucovorin | 30 mg/3 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Leucovorin | 50 mg/5 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| | | Leucovorin | 100 mg/10 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 5, 10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Leucovorin | 100 mg/10 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 200 mg/20 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| Leucovorin | 200 mg/20 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| Leucovorin | 300 mg/30 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 2, 3, 5, 10 |
| Leucovorin | 300 mg/30 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 2, 3, 5, 10 |
| Leucovorin | 10 mg/1 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 20 mg/2 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 30 mg/3 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 50 mg/5 ml | Solution for injection | IV, IM | Ampoule | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 100 mg/10 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 200 mg/20 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| Leucovorin | 250 mg/25 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |

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|---|---|---|---|---|---|---|---|---|
| | | Leucovorin | 300 mg/30 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| | | Leucovorin | 500 mg/50 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| | | Leucovorin | 900 mg/90 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| | | Leucovorin | 1000 mg/100 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1, 5, 10 |
| Greece | Wyeth Hellas SA<br>126 Kyprou 1 25th Martiou Str.<br>164 52 Athens<br>Greece | Leucovorin/Lederle | 100 mg/10 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1 |
| | | Leucovorin/Lederle | 200 mg/20 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1 |
| | | Leucovorin/Lederle | 30 mg | Powder for solution for injection | IV, IM | Vial | 30 mg | 1 |
| Ireland | Cyanamid of Great Britain LTD<br>Fareham Road<br>Gosport<br>Hampshire PO13 0AS<br>United Kingdom | Lederfolin | 350 mg/35 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1 |
| | | Lederfolin | 350 mg | Powder for solution for injection | IV, IM | Vial | 350 mg | 1 |
| | | Lederfolin | 15 mg | Powder for solution for injection | IV, IM | Vial | 15 mg | 1 |
| | | Lederfolin | 30 mg | Powder for solution for injection | IV, IM | Vial | 30 mg | 1 |
| | | Lederfolin | 3 mg/1 ml | Solution for injection | IV, IM | Ampoule | 3 mg/ml | 10 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Luxembourg | AHP Pharma S.A., Rue du Bosquet 15, 1348 Louvain la Neuve Belgium | Ledervorin Calcium | 3 mg/1 ml | Solution for injection | IV or IM | Ampoule | 3 mg/ml | 6 |
| | | Ledervorin Calcium | 50 mg/5 ml | Solution for injection | IV or IM | Ampoule | 10 mg/ml | 1, 10 |
| | | Ledervorin Calcium | 100 mg/10 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1, 10 |
| | | Ledervorin Calcium | 300 mg/30 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Ledervorin Calcium | 500 mg/50 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| Portugal | Teofarma s.r.l. Head Office : via F.lli Cervi 8 I-27010 Valle Salimbene (PV) Italy | Lederfoline | 5 mg/2 ml | Solution for injection | IV or IM | Ampoule | 2.5 mg/ml | 1 |
| | | Lederfoline | 50 mg/5 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Lederfoline | 100 mg/10 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Lederfoline | 200 mg/20 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Lederfoline | 300 mg/30 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Lederfoline | 350 mg/35 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| | | Lederfoline | 500 mg/50 ml | Solution for injection | IV or IM | Vial | 10 mg/ml | 1 |
| Spain | Wyeth Farma S.A. Ctra. Burgos, km 23 Devio Algete, km 1 28700 S. Sebastian de los Reyes Madrid, Spain | Lederfolin | 50 mg | Powder for solution for injection | IV or IM | Powder : Vial Water for injection : Ampoule | Powder : 50 mg Water for injection : 5 ml | 1 |
| | | Lederfolin | 350 mg | Powder for solution for injection | IV | Vial | 350 mg | 1 |
| | | Lederfolin | 3 mg/ 1 ml | Solution for injection | IM | Ampoule | 3 mg/1 ml | 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| United Kingdom | Cyanamid of Great Britain LTD<br>Fareham Road<br>Gosport<br>Hampshire PO3 0AS<br>United Kingdom | Lederfolin | 350 mg/35 ml | Solution for injection | IV, IM | Vial | 10 mg/ml | 1 |
| | | Lederfolin | 350 mg | Powder for solution for injection | IV, IM | Vial | 350 mg | 1 |
| | | Calcium Leucovorin | 15 mg | Powder for solution for injection | IV, IM | Vial | 15 mg | 1 |
| | | Calcium Leucovorin | 30 mg | Powder for solution for injection | IV, IM | Vial | 30 mg | 1 |
| | | Calcium Leucovorin | 3 mg/1 ml | Solution for injection | IV, IM | Ampoule | 3 mg/ml | 10 |

**ANNEX II**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

## SCIENTIFIC CONCLUSIONS

### OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LEDERFOLINE (and associated names - see Annex I)

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis in some cytotoxic therapy. It is a 50 year old product, mainly used under the supervision of medical oncologists.

France referred Lederfoline and associated names to the EMEA due to divergences of the nationally authorised summaries of product characteristics particularly with respect to the sections “indications”, “posology” and “contra-indications” of the summary of product characteristics.

On the basis of the grounds for referral, the point considered by the CPMP was a harmonisation of the Summaries of Product Characteristics, especially regarding the Therapeutic indications, the Posology and the Contraindications.

The following quality, efficacy and safety issues were addressed.

- Quality issues

No significant issues relating to Quality were identified and the pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC.

- Efficacy issues

Calcium folinate use with methotrexate therapy and in combination with 5-FU (especially in colorectal cancer) is considered well established even if various posologies exist, especially for the later. Calcium folinate is also recognised as antidote to the folic acid antagonists trimetrexate, trimethoprime, and pyrimethamine. Finally intravenous 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.

- Safety issues

The contraindication in case of pernicious anaemia or other anaemias due to vitamin B12 deficiency was acknowledged. The section on pregnancy and lactation was revised considering that recommendation mainly depends on the concommitant use with cytotoxic therapy. No other particular safety issues were raised but the wording of the sections on contra-indications, special warnings and precautions for use, interactions, pregnancy and lactation and undesirable effects were clarified and brought in line with the guideline on summary of product characteristics.

### Benefit/Risk considerations

Over 50 years, experience has been gained with the clinical use and safety of calcium folinate. Based on the documentation submitted by the Marketing Authorisation Holders and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of calcium folinate (solution for injection and powder for solution for injection) is positive for the agreed and harmonised indications.

## GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Lederfoline and associated names (see Annex I).

**ANNEX III**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**NOTE: THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL FOR ARBITRATION; THE TEXT WAS VALID AT THAT TIME.**

**IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT.**

## 1. NAME OF THE MEDICINAL PRODUCT

**<Lederfoline and associated names> <strength> <pharmaceutical form>**

(See Annex I – To be implemented nationally)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Each vial of <X ml> solution contains <Y mg/ml> of folinic acid provided as calcium folinate.>
<Each vial of powder contains <X mg> of folinic acid provided as calcium folinate. After reconstitution, the concentration is <Y mg/ml>.>

(See Annex I – To be implemented nationally)

*For excipients, see 6.1.*

## 3. PHARMACEUTICAL FORM

<Solution for Injection>
<Powder for Solution for Injection>

(See Annex I – To be implemented nationally)

## 4. CLINICAL PARTICULARS

*(The sections marked as […] are not applicable for the 3mg/ 1 ml and 5 mg/2 ml strengths.)*

### 4.1 Therapeutic indications

Calcium folinate is indicated

- to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as “Calcium Folinate Rescue”;
- [in combination with 5-fluorouracil in cytotoxic therapy.]

### 4.2 Posology and method of administration

For intravenous and intramuscular administration only. In the case of intravenous administration, no more than 160 mg of calcium folinate should be injected per minute due to the calcium content of the solution.

For intravenous infusion, calcium folinate may be diluted with 0.9% sodium chloride solution or 5% glucose solution before use. Refer also to sections 6.3 and 6.6.

*Calcium folinate rescue in methotrexate therapy:*
Since the calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of calcium folinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of calcium folinate.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

*Calcium folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Dosages above 25-50 mg should be given parenterally due to saturable enteral absorption of calcium folinate.*

Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m$^2$ body surface and should be considered with doses of 100 mg – 500 mg/m$^2$ body surface.

Dosage and duration of calcium folinate rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of calcium folinate is 15 mg (6-12 mg/m²) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Forty-eight hours after the start of the methotrexate infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is >0.5 µmol/l, calcium folinate dosages should be adapted according to the following table:

| Residual methotrexate blood level 48 hours after the start of the methotrexate administration: | Additional calcium folinate to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05 µmol/l: |
|---|---|
| ≥ 0.5 µmol/l | 15 mg/m² |
| ≥ 1.0 µmol/l | 100 mg/m² |
| ≥ 2.0 µmol/l | 200 mg/m² |

*[In combination with 5-fluorouracil in cytotoxic therapy:*
Different regimens and different dosages are used, without any dosage having been proven to be the optimal one.
The following regimens have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples. There are no data on the use of these combinations in children:

Bimonthly regimen: Calcium folinate 200 mg/m$^2$ by intravenous infusion over two hours, followed by bolus 400 mg/m$^2$ of 5-FU and 22-hour infusion of 5-FU (600 mg/m$^2$) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen: Calcium folinate 20 mg/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours plus 500 mg/m² 5-fluorouracil as i.v. bolus injection in the middle or at the end of the calcium folinate infusion.

Monthly regimen: Calcium folinate 20 mg/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy with 5-fluorouracil, modification of the 5-fluorouracil dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-fluorouracil. A reduction of calcium folinate dosage is not required.

The number of repeat cycles used is at the discretion of the clinician.]

*Antidote to the folic acid antagonists trimetrexate, trimethoprime, and pyrimethamine:*

Trimetrexate toxicity:

- Prevention: Calcium folinate should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Calcium folinate can be administered either by the intravenous route at a dose of 20 mg/m² for 5 to 10 minutes every 6 hours for a total daily dose of 80 mg/m², or by oral route with four doses of 20 mg/m$^2$ administered at equal time intervals. Daily doses of calcium folinate should be adjusted depending on the haematological toxicity of trimetrexate.

- Overdosage (possibly occurring with trimetrexate doses above 90 mg/m$^2$ without concomitant administration of calcium folinate): after stopping trimetrexate, calcium folinate 40 mg/m$^2$ IV every 6 hours for 3 days.

Trimethoprime toxicity:

- After stopping trimethoprime, 3-10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:

- In case of high dose pyrimethamine or prolonged treatment with low doses, calcium folinate 5 to 50 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

## 4.3 Contraindications

- Known hypersensitivity to calcium folinate, or to any of the excipients.
- Pernicious anaemia or other anaemias due to vitamin $B_{12}$ 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

**Calcium folinate 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*

Calcium folinate should be used with methotrexate [or 5-fluorouracil] only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Calcium folinate treatment may mask pernicious anaemia and other anaemias resulting from vitamin $B_{12}$ 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 calcium folinate administration and after discontinuation is recommended (see also section 4.5 Interactions).

*[Calcium folinate/5-fluorouracil*
Calcium folinate 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 calcium folinate 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/calcium folinate 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.

Calcium folinate 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/calcium folinate treatment and calcium supplementation should be provided if calcium levels are low.]

*Calcium folinate/methotrexate*
For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.

Calcium folinate 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 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.

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 calcium folinate rescue increases, calcium folinate 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 calcium folinate 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.

Calcium folinate 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 calcium folinate 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 calcium folinate 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 calcium folinate to diminish toxicity or counteract the effects.

[5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breast-feeding; this applies also to the combined use of calcium folinate 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 calcium folinate is excreted into human breast milk. Calcium folinate 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 calcium folinate has an effect on the ability to drive or use machines.

## 4.8 Undesirable effects

*[Both therapeutic indications:]*

Immune system disorders

*Very rare (<0.01%): allergic reactions, including anaphylactoid 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 calcium folinate 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:

Monthly regimen:

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

General disorders and administration site conditions
Very common (>10%): (severe) mucosal toxicity.

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 calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

[Should overdosage of the combination of 5-fluorouracil and calcium folinate 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: V03AF03

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis in cytotoxic therapy.

Calcium folinate is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Calcium folinate and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. It also protects cells from the effects of folate antagonist by repletion of the reduce folate pool. Calcium folinate serves as a pre-reduced source of H4 folate; it can therefore bypass folate antagonist blockage and provide a source for the various coenzyme forms of folic acid.

[Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and calcium folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5FU-TS complex and increasing activity.]

Finally intravenous 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. This may be the case during total parenteral nutrition and severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia due to folic acid deficiency, when oral administration is not feasible.

## 5.2 Pharmacokinetic properties

Absorption
Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels ($C_{max}$) are achieved.

Metabolism
Calcium folinate is a racemate where the L-form (L-5-formyl-tetrahydrofolate, L-5-formyl-THF), is the active enantiomer.

The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Distribution
The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after i.v. administration.

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4±3.5 mg.min/l and 129±112 mg.min/l after a dose of 25 mg. The inactive D-isomer is present in higher concentration than L-5-formyl-tetrahydrofolate.

Elimination
The elimination half-life is 32 - 35 minutes for the active L-form and 352 - 485 minutes for the inactive D-form, respectively.

The total terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).

Excretion
80-90 % with the urine (5- and 10-formyl-tetrahydrofolates inactive metabolites), 5-8 % with the faeces.

## 5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

(To be implemented nationally)

### 6.2 Incompatibilities

Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, fluorouracil, foscarnet and methotrexate.

**Droperidol**
1. Droperidol 1.25 mg/0.5 ml with calcium folinate 5 mg/0.5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25° C followed by 8 minutes of centrifugation.

2. Droperidol 2.5 mg/0.5 ml with calcium folinate 10 mg/0.5 ml, immediate precipitation when the drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

**Fluorouracil**
Calcium folinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/ml with calcium folinate 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.

**Foscarnet**
Foscarnet 24 mg/ml with calcium folinate 20 mg/ml formation of a cloudy yellow solution reported.

### 6.3. Shelf life

(To be implemented nationally)

### 6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator).
Do not store above 25°C.
Store in original container to protect from light.

*(To be implemented nationally)*

### 6.5 Nature and contents of container

(See Annex I – To be implemented nationally)

Not all pack sizes may be marketed.

### 6.6 Instructions for use and handling and disposal

Prior to administration, calcium folinate should be inspected visually. The solution for injection or infusion should be a clear and yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded. Calcium folinate solution for injection or infusion 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

(See Annex I – To be implemented nationally)

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT