Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Folinic acid (as calcium folinate) Actavis 10mg/ml solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 10.8 mg of calcium folinate, equivalent to 10 mg folinic acid.

One 3 ml vial contains 32.4 mg of calcium folinate equivalent to 30 mg folinic acid.
One 10 ml vial contains 108 mg of calcium folinate equivalent to 100 mg folinic acid.

Excipient with known effect:
Contains 3.05 mg/ml sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calcium folinate is used 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 (5-FU) in cytotoxic therapy.

4.2 Posology and method of administration

Posology

Calcium folinate rescue in methotrexate therapy:
Since the calcium folinate rescue dosage regimen heavily depends 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 for a calcium folinate rescue dosage regimen used in adults, elderly and children:

Calcium folinate rescue in intermediate- and high-dose methotrexate therapy:
Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m^2 body surface and has to be considered with doses of 100 mg – 500 mg/m^2 body surface.

Dosage and duration of use of calcium folinate primarily depend on the type and dosage of methotrexate therapy and/or on the occurrence of toxicity symptoms and the individual excretion capacity for methothrexate. As a rule, the first dose of calcium folinate is 15 mg (6-12 mg/m^2) 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 rapid 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 by measuring serum creatinine levels daily.
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 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 dosage. The following regimens have been used in adults and the elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples. There are no data on the use of calcium folinate in combination with 5-fluorouracil in children:

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

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

Monthly regimen: once a month during 5 consecutive days: 20 mg/m^2 by bolus intravenous injection or 200 to 500 mg/m² as intravenous infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as intravenous bolus injection.

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 intravenously at a dose of 20mg/m² for 5 to 10 minutes every 6 hours (total daily dose of 80mg/m²), or orally with four doses of 20mg/m² administered at equal time intervals. Daily doses of calcium or calcium folinate should be adjusted depending on the haematological toxicity of trimetrexate.
- Over dosage (possibly occurring with trimetrexate doses above 90mg/m² without concomitant administration of calcium folinate): Calcium folinate should be administered intravenously at a dose of 40mg/m² every 6 hours for 3 days, following cessation of treatment with trimetrexate.

Trimethoprime toxicity:

- Following cessation of treatment with trimethoprime, calcium folinate should be administered intravenously at a dose of 3-10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:
- In cases 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

Method of administration

Calcium folinate is administered parenterally as intramuscular injection or intravenous injection or infusion. Do not administer calcium folinate intrathecally.

Death has been reported when folinic acid has been administered intrathecally, following intrathecal overdose of methotrexate.

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.

As a rule calcium folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders (vomiting, diarrhoea, subileus etc.) where enteral absorption is not assured. Dosages above 25-50 mg should be given parenterally due to saturable enteral absorption of calcium folinate.

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.

4.3 Contraindications

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

Calcium folinate should not be used for the treatment of pernicious anaemia or other megaloblastic anaemias caused by vitamin B12 deficiency.
For the use of calcium folinate with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6 and the summaries of product characteristics for methotrexate- and 5-fluorouracil- containing medicinal products.

4.4 Special warnings and precautions for use

General:

Calcium folinate should only be administered parenterally as intramuscular injection or intravenous injection or infusion. Do not administer calcium folinate intrathecally.

Death has been reported when folinic acid has been administered intrathecally, following intrathecal overdose of methotrexate.

Calcium folinate should only be used with methotrexate or 5-fluorouracil 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 B12 deficiency.

Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors (hydroxycarbamide, cytarabine, mecaptopurine, thioguanine)– lead to macrocytosis. Such a macrocytosis is not considered to be treated by folinic acid.

In epileptic patients treated with phenobarbital, phenytoine, primidone, and succinimides there is a risk to increase the frequency of seizures due to 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 section 4.5).

Calcium folinate/methotrexate:

For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.

Calcium folinate has no effect on non-hematological 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 other toxicities associated with methotrexate (please refer to the Summary of Product Characteristics 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 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 folinate antagonist, such as methotrexate, should be treated as a medicinal emergency. As the time interval between methotrexate administration and Calcium Folinate Rescue increases, the effectiveness of calcium folinate to counteract the toxicity decreases.

The possibility that the patient is taking other medications that interact with methotrexate (eg. medication which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

Calcium folinate/5-fluorouracil:

In combination regimen with 5-fluorouracil, 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.
In cases of toxicity when calcium folinate and 5-fluorouracil are used in combination, the 5-fluorouracil dosage should be reduced more than in cases of toxicity 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 stomatitits occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared. 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 folinate must not be mixed with 5-fluorouracil in the same intravenous 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.

This medicinal product contains 3.05 mg sodium per ml, that is 9.15 mg per 3 ml vial and 30.5 mg per 10 ml vial. To be taken into consideration by patients on a controlled sodium diet.

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 anticonvulsivant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also section 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 Fertility, 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 is no indication that folinic 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 folinate 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.

Breastfeeding
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

No studies on the effects on the ability to drive and use machines have been performed. Calcium folinate is however not expected to affect the ability.

4.8 Undesirable effects

Both therapeutic indications:

Immune system disorders
Very rare (<1/10,000): allergic reactions, including anaphylactoid / anaphylactic reactions, and urticaria.

Psychiatric disorders
Rare (≥1/10,000 to <1/1,000): insomnia, agitation and depression after high doses.

Nervous system disorders
Rare (≥1/10,000 to <1/1,000): increase in the frequency of attacks in epileptics (see also section 4.5).

Gastrointestinal disorders
Rare (≥1/10,000 to <1/1,000): gastrointestinal disorders after high doses.

General disorders and administration site conditions
Uncommon (≥1/1,000 to <1/100): 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:

Metabolism and Nutritional disorder
Not known (cannot be estimated from the available data): Hyperammonaemia

Blood and lymphatic system disorders
Very common (≥1/10): bone marrow failure, including fatal cases.

General disorders and administration site conditions
Very common (≥1/10): mucositis, including stomatitis and chelitis. Fatalities have occurred as a result of mucositis.

Skin and subcutaneous tissue disorders
Common (≥1/100 to <1/10): Palmar-Plantar Erythrodysaesthesia

Monthly regimen:

Gastrointestinal disorders
Very common (≥1/10): vomiting and nausea

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

Weekly regimen:

Gastrointestinal disorders
Very common (≥1/10): diarrhoea 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more calcium folinate than the recommended dosage.
Should overdosage of the combination of 5-fluorouracil with calcium folinate occur, follow the overdosage instructions for 5-fluorouracil.

Excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: V03AF03
Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment.

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and 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. Calcium folinate also protects cells from the effects of folate antagonists by repletion of the reduced 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 form as of folic acid.

Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-fluorouracil) to enhance its cytotoxic activity. 5-fluorouracil inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosyntheses, and calcium folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5-fluorouracil-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 oral administration of folic acid. 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 application of the aqueous solution, systemic availability is comparable to an intravenous application. However, lower peak serum levels (C_{max}) are achieved.

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-formyltetrahydrofolate.

Biotransformation
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.

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

Preclinical test results showed no risks not previously known from clinical experience (see other sections of the SPC).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injections

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 was observed after direct admixture in a syringe for 5 minutes at 25^{o}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 was observed when the drugs were injected sequentially into a Y-connector 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^{o}C, 23^{o}C, or 32^{o}C in polyvinyl chloride containers.

Foscarnet
The formation of a cloudy yellow solution has been reported when Foscarnet 24 mg/ml is mixed with with calcium folinate 20 mg/ml.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Shelf-life after dilution
Chemical and physical in-use stability after dilution in 5% glucose solution or 0.9 % sodium chloride solution has been demonstrated for 24 hours at 15°C to 25°C and normal light exposure.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Brown vials (type I glass) with bromobutylic rubber stopper and aluminium metallic cap with a polypropylene disc.

Package sizes:
1 x 3 ml vial
5 x 3 ml vial

1 x 10 ml vial
5 x 10 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If necessary Folinic acid Actavis may be diluted with the following solutions for infusion: 5 % glucose solution or 0.9 % sodium chloride solution**.**

The medicinal product is for single use only. Any unused solution should be discarded. The solution for injection should be inspected visually prior to use. Only clear solutions without particles should be used**.** If cloudy in appearance or particles are observed, the solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/120/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th May 2011

Date of last renewal: 4th November 2015

10 DATE OF REVISION OF THE TEXT

September 2016