DBL™ LEUCOVORIN CALCIUM INJECTION (CALCIUM FOLINATE)

1. NAME OF THE MEDICINE

Calcium folinate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Leucovorin Calcium Injection vial 300 mg/30 mL contains 300 mg folinic acid (as calcium folinate).

Excipients with known effects
DBL Leucovorin Calcium Injection 300 mg/30 mL contains 8.5 mg/mL of sodium chloride.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

DBL Leucovorin Calcium Injection is a clear straw-to pale yellow coloured sterile, isotonic solution free from visible particular matter. The solution does not contain a bactericide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Folinic acid has shown good results in the treatment of certain megaloblastic anaemias resulting from folic acid deficiency. This mainly occurs in infants, during pregnancy, in malabsorption syndromes, liver diseases, sprue and malnutrition. It is not more effective than folic acid for these conditions.

Folinic acid has also shown good results in reducing the toxicity and circumventing the effect of folic acid antagonists, if therapeutically desired.

4.2 Dose and method of administration

Dosage

DBL Leucovorin Calcium rescue after methotrexate therapy

The recommendations for DBL Leucovorin Calcium rescue are based on a methotrexate dose of 12 to 15 g/m^2 administered by intravenous infusion over four hours (see Product Information for methotrexate). DBL Leucovorin Calcium rescue at a dose of 15 mg (approximately 10 mg/m^2) every six hours for ten doses starts 24 hours after the beginning of the methotrexate infusion.

In the presence of gastrointestinal toxicity, nausea or vomiting, DBL Leucovorin Calcium should be administered parenterally. Serum creatinine and methotrexate levels should be determined at least once daily. DBL Leucovorin Calcium Injection administration, hydration and urinary alkalinisation (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy.

The DBL Leucovorin Calcium dose should be adjusted or folinic acid rescue extended based on the following guidelines shown in Table 1.

Table 1: Guidelines for DBL Leucovorin Calcium dosage and administration

Clinical situation/laboratory findings	DBL Leucovorin Calcium dosage and duration
Normal methotrexate elimination Serum methotrexate level approximately 10 μM at 24 hours after administration, 1 μM at 48 hours, and less than 0.2 μM at 72 hours.	15 mg intramuscularly or intravenously every six hours for 60 hours (ten doses starting at 24 hours after start of methotrexate infusion).
Delayed methotrexate elimination Serum methotrexate level remaining above 0.2 μM at 72 hours, and more than 0.05 μM at 96 hours after administration.	Continue 15 mg intramuscularly or intravenously every six hours until methotrexate level is less than 0.05 μM.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate DBL Leucovorin Calcium therapy, these patients require continuing hydration and urinary alkalinisation and close monitoring of fluid and electrolyte status until the serum methotrexate level has fallen to below 0.05 μM and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration which are significant but less severe than the abnormalities described above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, DBL Leucovorin Calcium rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Note. The above dosage recommendations do not necessarily apply to experimental high dose methotrexate therapy. High dose methotrexate therapy should only be administered by qualified specialists and in hospitals where the necessary facilities are available. Recent published literature should be consulted for details at all times.

Impaired methotrexate elimination or inadvertent overdosage

In the treatment of accidental overdosage of folic acid antagonists, e.g., methotrexate, DBL Leucovorin Calcium should be administered as promptly as possible. As the time interval between antifolate administration and DBL Leucovorin Calcium rescue increases, DBL Leucovorin Calcium's effectiveness in counteracting toxicity diminishes.

Monitoring of serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with DBL Leucovorin Calcium. Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of DBL Leucovorin Calcium or prolonged administration may be indicated. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended. Doses higher than those recommended for oral use must be given intravenously.

DBL Leucovorin Calcium rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion.

DBL Leucovorin Calcium 10 mg/m^2 should be administered intravenously, intramuscular every six hours until the serum methotrexate level is less than 0.01 μM.

In the presence of gastrointestinal toxicity, nausea or vomiting, DBL leucovorin calcium should be administered parenterally. Serum creatinine and methotrexate levels should be determined at intervals of 24 hours. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 μM or the 48 hour level is greater than 0.9 μM, the dose of leucovorin calcium should be increased to 100 mg/m^2 intravenously every three hours until the methotrexate level is less than 0.01 μM.

Hydration (3 L/day) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Treatment of megaloblastic anaemias

Solution for injection
Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Treatment of pyrimethamine overdosage

The dosage of pyrimethamine in treating toxoplasmosis is 10 to 20 times its dosage for malaria and approaches the toxic level. Since DBL Leucovorin Calcium is not utilised by protozoa, it can be given simultaneously without impairing the effectiveness of therapy. The usual dosage is 3 to 9 mg/day by intramuscular injection for three days or until the platelet and leucocyte counts have reached safe levels.

Method of administration

DBL Leucovorin Calcium Injection may be given parenterally by intramuscular injection, intravenous injection or intravenous infusion. DBL Leucovorin Calcium Injection should NOT be administered intrathecally. When DBL Leucovorin Calcium Injection has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported (see Section 4.4 Special warnings and precautions for use).
Because of the calcium ion content of the Calcium folinate injections, no more than 160 mg (16 mL of the 300 mg/30 mL formulation), should be injected intravenously per minute.

DBL Leucovorin Calcium Injection contains no antimicrobial agent. This product is for single use in one patient only.

When required for intravenous infusion, DBL Leucovorin Calcium Injection may be diluted in 1 litre of 5% w/v glucose solution or 0.9% sodium chloride solution. The diluted solutions are stable for 24 hours when stored between 2°C to 8°C. However, to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the solution. Infusion should be completed within 24 hours and any unused solution should be discarded.

Admixed solutions for parenteral administration should be visually inspected for particulate matter and discolouration prior to administration where solution and container permit. Do not use if solution is cloudy or precipitated.

Patient monitoring Laboratory tests

Methotrexate/folinic acid therapy

Patients being treated with DBL Leucovorin Calcium following methotrexate therapy, including inadvertent overdose, or patients with impaired methotrexate elimination, should have serum creatinine and methotrexate levels determined at intervals of 24 hours. In cases of methotrexate overdose or delayed excretion, monitor urine pH as appropriate, to ensure maintenance of pH $\geqslant$ 7.0.

DBL Leucovorin Calcium dosage should be adjusted on the basis of laboratory test results.

5-Fluorouracil/folinic acid therapy

Complete blood count (CBC) with differential and platelets: Prior to each treatment; weekly during the first two courses; at time of anticipated white blood cell (WBC) nadir in all courses thereafter.

Electrolytes and liver function tests: prior to each treatment for the first three courses and prior to every other course thereafter.

4.3 Contraindications

DBL Leucovorin Calcium therapy is contraindicated in patients with:

Pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B_{12}. When treating these conditions with folinic acid, haematological remission may occur, but neurological manifestations are likely to progress.

Known hypersensitivity to the active substance(s) or to any of the excipients.

4.4 Special warnings and precautions for use

DBL Leucovorin Calcium Injection should be administered only by intramuscular or intravenous injection and must not be administered intrathecally. **When DBL Leucovorin Calcium Injection has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported (see Section 4.2 Dose and method of administration).**

General

Folinic acid should only be used with folic acid antagonists, e.g. methotrexate, or fluoropyrimidines, e.g. fluorouracil, under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb folinic acid,

Simultaneous therapy with a folic acid antagonist and folinic acid is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited. See Section 4.5 Interactions with other medicines and other forms of interactions.

Many cytotoxic medicinal products - direct or indirect DNA synthesis inhibitors - lead to macrocytosis (hydrocarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. See Section 4.8 Adverse effects (undesirable effects), Nervous system disorders.

Since three patients had recurrent neurological symptoms on rechallenge with folinic acid further treatment with folinic acid is not recommended in these circumstances.

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 folinic acid administration and after discontinuation is recommended. (See Section 4.5 Interactions with other medicines and other forms of interactions.)

Folinic acid/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 folinic acid rescues increases, folinic acid effectiveness in counteracting toxicity decreases.

Folinic acid has no effect on non-haematological toxicities of methotrexate, such as nephrotoxicity resulting from drug 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 health-care professional labeling 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 folinic acid.
Excessive folinic acid doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where folinic acid accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies resistance to folinic acid rescue as both medicinal products share the same transport system.

Folinic Acid/Fluorouracil

Folinic acid must not be mixed with fluorouracil in the same IV injection or infusion. Folinic acid may enhance the toxicity profile of fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. In addition, hematological adverse reactions have been observed. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving fluorouracil and folinic acid. Concomitant granulocytopenia and fever were present in some but not all patients. When folinic acid and fluorouracil are used in combination, in cases of toxicity the fluorouracil dosage has to be reduced more than when fluorouracil is used alone.

Combined folinic acid/fluorouracil treatment should not be initiated or maintained in patients with symptoms of gastrointestinal (GI) toxicity, regardless of the severity, until all of these symptoms have completely disappeared. Because diarrhoea may be a sign of GI toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of fluorouracil until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of fluorouracil.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases.

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

Use in the elderly

Elderly patients are at increased risk of severe toxicity when receiving combination therapy of folinic acid and fluorouracil. Particular care should be taken when treating these patients.

Paediatric use

There are no data available on use in children.

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin, primidone and succinimides, and increase the frequency of seizures in susceptible children, and 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 Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during folinic acid administration and after discontinuation.

High intravenous or intramuscular doses of folinic acid may reduce the efficacy of intrathecally administered methotrexate.

Folinic acid may enhance the toxicity of fluorouracil. When folinic acid is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect) the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

Concurrent administration of chloramphenicol and folic acid in folate deficient patients may result in antagonism of haematopoietic response to folic acid. Folinic acid may enhance the toxicity of fluorouracil (see Sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy - Category A

There are no adequate and well-controlled clinical studies conducted in pregnant or breastfeeding woman. No formal animal reproductive toxicity studies with folinic acid have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, 5-flurouracil and 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 fetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of folinic acid to diminish toxicity or counteract the effects.

Fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of folinic acid with fluorouracil.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when folinic acid is administered to a breastfeeding mother.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Allergic sensitisation, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folinic acid. Nausea and vomiting with very high doses of folinic acid have been reported.

In addition, haematological adverse reactions, such as leucocytopenia, neutropenia, anaemia and thrombocytopenia, may occur. These adverse reactions are dose dependent and their occurrence can usually be decreased by reducing the dosage of cytotoxic drugs. To control these adverse reactions, haematological values e.g. blood leucocyte and thrombocyte levels, and serum electrolyte (e.g. Na, K, Ca) and creatinine levels should be closely monitored.

Immune system disorders
Frequency undetermined: Hypersensitivity
Very rare (<0.1%): Anaphylactoid/anaphylactic reactions and anaphylactic shock.

Psychiatric disorders
Rare (0.01 – 0.1%): Insomnia, agitation and depression after high doses.

Nervous system disorders
Rare (0.01 – 0.1%): Increase in the frequency of attacks in epileptics patients (also see Section 4.5 Inetractions with medicines and other types of interactions), seizures and/or syncope.

Skin and subcutaneous tissue disorders
Frequency undetermined: Urticaria.

Gastrointestinal disorders
Rare (0.01 – 0.1%): Gastrointestinal disorders after high doses, abdominal pain

General disorders and administrations site conditions
Uncommon (0.1-1%):: Pyrexia after administration of DBL Leucovorin Calcium Injection.

Cases of Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving folinic acid in combination with other agents known to be associated with these disorders. A contributory role of folinic acid in these occurrences of SJS/TEN cannot be excluded.

Folinic Acid in combination with fluorouracil

Generally the safety profile of folinic acid depends on the applied regimen of fluorouracil due to enhancement of fluorouracil-induced toxicities.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration (see Section 4.4 Special warnings and precautions for use).

Additional undesirable effects of folinic acid when used in combination with fluorouracil are listed below:
Metabololisn and nutrition disorders
Frequency undetermined: Hyperammonaemia

Blood and lymphatic system disorders
Very common (>10%): bone marrow failure, including fatal cases.

General disorders and administration site condition
Very common (>10%):: Mucositis, Fatalities have occurred as a result of mucositis.

Skin and subcutaneous tissue disorders
Common (1-10%):: Palmar-Palmar Erythrodysaesthesia syndrome (hand-foot syndrome)

Gastrointestinal disorders
Very common (>10%): Nausea and vomiting, diarrhoea, stomatitis, cheilitis.

The most common dose limiting adverse reaction occurring in patients receiving a combination of folinic acid and fluorouracil are stomatitis and diarrhoea.

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhoea) and myelosuppression. In patients with diarrhoea, rapid clinical deterioration leading to death can occur (see Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Folinic acid is an intermediate in the metabolism of folinic acid and can therefore be considered as a naturally occurring substance. Large doses have been administered with no apparent adverse effects. Such doses suggest that administration of this drug is relatively safe. Signs of excessive dosing, if they occur, should be treated symptomatically.

Excessive amounts of folinic acid nullify the chemotherapeutic effect of folic acid antagonists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Folinic acid is the formyl derivative of tetrahydrofolic acid which is a metabolite and active form of folic acid. Folinic acid as a co-factor participates in many metabolic reactions including purine synthesis, pyrimidine synthesis and amino acid conversion. It is effective in the treatment of megaloblastic anaemia caused by folic acid deficiency and is a potent antidote for both the haematopoietic and reticuloendothelial toxic effects of folic acid antagonists, e.g. methotrexate, pyrimethamine, trimethoprim. Folinic acid is used in cytotoxic therapy as an antidote to folic acid antagonists which block conversion of folic acid to tetrahydrofolate by binding enzyme dihydrofolate reductase. In some cancers, folinic acid enters and 'rescues' normal cells, in preference to tumor cells, from the toxic effects of folic acid antagonists, due to a difference in membrane transport mechanism. This principle is applied in high-dose methotrexate therapy with 'folinic acid rescue'.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following administration, folinic acid enters the general body pool of reduced folates. It has been reported that, following intravenous, intramuscular administration, peak serum level of total reduced folates are achieved within a mean time of 10 minutes, 52 minutes and 1.7 hours, respectively. Peak levels of 5-formyl THF appear at 10 minutes and 28 minutes following intravenous and intramuscular administration respectively.

Distribution

Folate is concentrated in the cerebrospinal fluid and liver although distribution occurs to all body tissues. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

Metabolism

Calcium folinate is rapidly and extensively converted to 5-methyl tetrahydrofolate (an active metabolite) *in vivo*, with less extensive conversion resulting from parenteral administration.

Reduction in the levels of parent compound coincides with the appearance of the active metabolite 5- methyl THF, which becomes the major circulating form of the drug. Peak levels are observed at 1.5 and 2.8 hours following intravenous and intramuscular administration respectively. The terminal half-life for total reduced folates is reported as 6.2 hours. Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver and found in moderate amounts in the CSF. Following a 15 mg dose given either orally or intramuscularly, peak serum folate concentrations of 0.268 micrograms/mL and 0.241 micrograms/mL were detected.

Excretion

Folinic acid is eliminated mainly as 10-formyl tetrahydrofolate and 5,10-methyl tetrahydrofolate. The metabolites are mainly excreted via the urine (80-90%), with elimination being logarithmic in doses exceeding 1 mg.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Water for injection

Sodium hydroxide and/or hydrochloric acid (used to adjust pH of 300 mg/30 mL).

6.2 Incompatibilities

Folinic acid has been reported to be incompatible with injectable forms of methotrexate, fluorouracil droperidol, fosacarnet and phosphonosulphate.

For more information refer to 'Section 4.5 Interactions with other medicines and other forms of interactions'

6.3 Shelf life

Please refer to outer carton for the expiry date.

6.4 Special precautions for storage

Please refer to outer carton for the storage condition. (Refrigerate. Do not freeze). Protect from light.

6.5 Nature and contents of container

DBL Leucovorin Calcium Injection 300 mg/30 mL is supplied in a 30 mL Type 1 clear glass vial with a chlorobutyl rubber stopper in packs of one vial per pack.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed per local regulations.

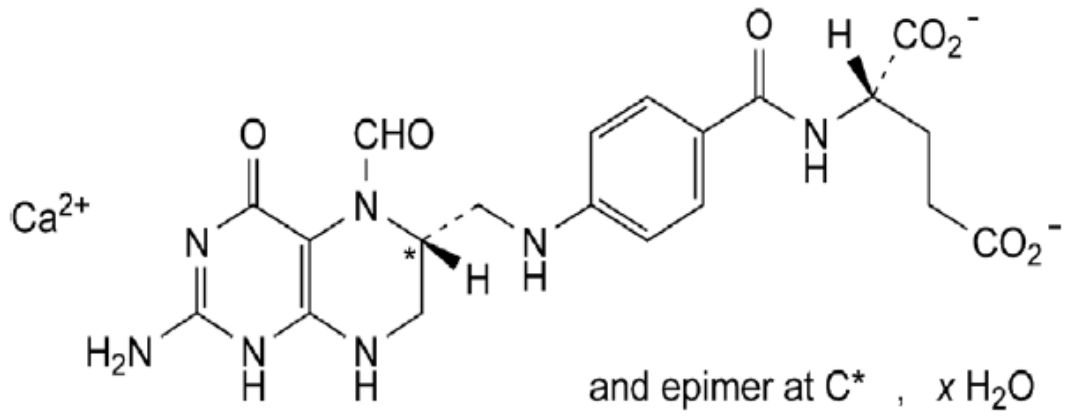
6.7 Physicochemical

Calcium folinate is a white to light yellow, amorphous or crystalline hygroscopic powder.

Sodium chloride is included for isotonicity.

Chemical structure

The chemical structure of calcium folinate is shown below:



Chemical name: Calcium (2S)-2-[[4-[[[(6RS)-2-amino-5-formyl-4-oxo1,4,5,6,7,8 hexahydropteridin-6-yl]methyl]amino]benzoyl]amino]pentanedioate

Chemical Formula: $C_{20}H_{21}CaN_7O_7,xH_2O$

The chemical formula is $C_{20}H_{21}CaN_7O_7,xH_2O$ and the molecular weight of anhydrous calcium folinate is 511.5.

CAS number

2060570-47-8.

Pfizer Corporation Hong Kong Limited
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