Teva Pharmaceuticals (Pty) Ltd.	**Product name: Leucovorin 100 mg/10 ml; 200 mg/20 ml; 300 mg/30 ml Abic** **Dosage Form & strength:** Each vial contains leucovorin calcium pentahydrate equivalent to leucovorin (acid) anhydrous 100 mg; 200 mg; 300 mg, respectively (10 mg/ml)

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S1

PROPRIETARY NAME AND DOSAGE FORM:

LEUCOVORIN 100 mg/10 ml ABIC

LEUCOVORIN 200 mg/20 ml ABIC

LEUCOVORIN 300 mg/30 ml ABIC

COMPOSITION:

LEUCOVORIN 100 mg/10 ml ABIC:

Each vial contains Leucovorin calcium pentahydrate equivalent to 100 mg Leucovorin (acid) (10 mg/ml).

LEUCOVORIN 200 mg/20 ml ABIC:

Each vial contains Leucovorin calcium pentahydrate equivalent to 200 mg Leucovorin (acid) (10 mg/ml).

LEUCOVORIN 300 mg/30 ml ABIC:

Each vial contains Leucovorin calcium pentahydrate equivalent to 300 mg Leucovorin (acid) (10 mg/ml).

PHARMACOLOGICAL CLASSIFICATION:

A 8.3 Erythopoietics (Haematinics)

PHARMACOLOGICAL ACTION:

Leucovorin is the formyl derivative of tetrahydrofolic acid, the metabolite of folic acid, and an essential coenzyme for nucleic acid synthesis. It is readily converted to other folic acid derivatives and replaces folic acid lost because of deficiency on administration of folic acid antagonists. It readily crosses the blood brain barrier and is stored primarily in the liver.

INDICATIONS:

To diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy. This procedure is commonly known as calcium leucovorin rescue.

Amelioration of the blood picture in a number of megaloblastic anaemias due to folate deficiency.

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CONTRAINDICATIONS:

Known hypersensitivity to the preparation.

Calcium leucovorin should not be used as the sole antianaemic agent in the presence of pernicious anaemia or vitamin B_{12} deficiency. It must not be used in the treatment of pernicious anaemia or other megaloblastic anaemias secondary to lack of vitamin B_{12} since it may produce a haematologic remission while neurologic manifestations continue to progress.

WARNINGS:

If methotrexate is administered intrathecally as local therapy and leucovorin calcium is administered concurrently, the presence of tetrahydrofolate may negate the antineoplastic effect of methotrexate.

Leucovorin intensifies the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of 5-fluorouracil must be lowered. Therapy with leucovorin/5-fluorouracil must not be initiated or continued in patients who have symptoms of gastro-intestinal toxicity of any severity. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving this combination. Patients with diarrhoea must be monitored with particular care.

Leucovorin may increase the frequency of seizures in susceptible children by counteracting the anticonvulsant effects of barbiturates, hydantoin anticonvulsants and primidone.

Leucovorin calcium for injection and lyophilised powder for injection, when diluted with a diluent containing benzyl alcohol should not be used in premature or newborn infants.

DOSAGE AND DIRECTIONS FOR USE:

Megaloblastic anemia secondary to folate deficiency

A dosage of 1 – 15 mg daily may be administered intramuscularly.

Calcium Leucovorin Rescue

LEUCOVORIN* Rescue schedules following high-dose methotrexate		
Methotrexate plasma level	**Leucovorin dose**	**Duration of Leucovorin therapy**
Less than 5×10^{-6} M (24 hours after a 6-hour infusion)	10 to 15 mg/m^2 every 6 hours	48 – 72 hours
For every logarithmic concentration of methotrexate higher than 10^{-6} M, raise the dose of Leucovorin by a factor of 10 every 3 to 6 hours, until methotrexate levels fall below 10^{-8} M. (at 24 – 30-hour post-infusion)		
Less than 1.5×10^{-6} M	10 to 15 mg/m^2 every 6 hours	48 hours
1.5 to 5×10^{-6} M	30 mg/m^2 every 8 hours	Until methotrexate level is less than 10^{-8} M

5 x 10^{-6} M	60 to 100 mg/m^2 every 6 hours	Until methotrexate level is less than 10^{-8} M

In general up to 120 mg are usually given in divided doses, over 12 – 24 hours by intramuscular injection, bolus intravenous injection, or intravenous infusion in 0,9 % m/v sodium chloride solution, followed by 12 – 15 mg intramuscularly, or 15 mg orally, every six hours for the next 48 hours.

In general, it is recommended that administration of Leucovorin be consecutive rather than simultaneous with methotrexate administration so as not to interfere with methotrexate's antineoplastic effects, usually within the first 36 to 42 hours of starting methotrexate infusion, in a dosage that will produce blood levels equal to or greater than methotrexate blood levels.

Duration of leucovorin treatment also varies with the dosage of methotrexate and in patients with renal function impairment or pleural or peritoneal effusions.

Intravenous solutions containing leucovorin calcium in 10 % dextrose solution, 10 % dextrose in sodium chloride injection, lactated Ringer's injection, or Ringer's injection have been found to maintain at least 90 % of labelled potency when used within 24 hours.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The following adverse reactions may occur: pyrexia, hives, itching, rash, wheezing (hypersensitivity reaction). Thrombocytosis has been reported in patients receiving leucovorin during intra-arterial infusion of methotrexate.

When used as a rescue from the effects of methotrexate, LEUCOVORIN ABIC should be used with caution in the presence of renal function impairment or pleural or peritonial effusions, since such problems may effect the excretion of methotrexate. Patients receiving LEUCOVORIN ABIC as a rescue from the toxic effects of methotrexate should be under the supervision of a doctor experienced in high-dose methotrexate therapy.

LEUCOVORIN ABIC should never be given alone or in conjunction with inadequate amounts of hydroxy-cobalamin for the treatment of pernicious anemia.

The following checks are important in-patient monitoring when LEUCOVORIN ABIC is used as a rescue in high-dose methotrexate therapy:

Creatinine Clearance:

This should be performed prior to initiation of high-dose methotrexate therapy.

Plasma Methotrexate Levels: (approximately 48 hours after methotrexate administration) To determine the duration of LEUCOVORIN ABIC treatment needed to maintain rescue. If levels are too high, repeat every 24 hours until normal.

Serum Creatinine Determinations:

This is recommended daily to detect developing renal dysfunction.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See “Side-effects and Special Precautions”. Treatment is symptomatic and supportive.

IDENTIFICATION:

LEUCOVORIN 100 mg/10 ml ABIC:

A clear yellow solution free of particulate matter.

LEUCOVORIN 200 mg/20 ml ABIC:

A clear yellow solution free of particulate matter.

LEUCOVORIN 300 mg/30 ml ABIC:

A clear yellow solution free of particulate matter.

PRESENTATION:

LEUCOVORIN 100 mg/10 ml ABIC:

A clear glass vial containing 10 ml of solution.

LEUCOVORIN 200 mg/20 ml ABIC:

A clear glass vial containing 20 ml of solution.

LEUCOVORIN 300 mg/30 ml ABIC:

A clear glass vial containing 20 ml of solution.

STORAGE INSTRUCTIONS:

LEUCOVORIN ABIC is to be stored in a refrigerator (2 – 8 ºC) and protected from light.

Do not freeze.

REGISTRATION NUMBERS:

LEUCOVORIN 100 mg/10 ml ABIC: 27/8.3/0151

LEUCOVORIN 200 mg/20 ml ABIC: 27/8.3/0152

LEUCOVORIN 300 mg/30 ml ABIC: 27/8.3/0153

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NAME AND ADDRESS OF THE APPLICANT:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

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Gauteng

South Africa

2090

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