Teva Pharmaceuticals (Pty) Ltd.	**Product:** **Leucovorin 100 mg/10 ml; 200 mg/20 ml; 300 mg/30 ml Abic** **Dosage Form:** Vial **Strength:** Each vial contains leucovorin calcium pentahydrate equivalent to leucovorin (acid) anhydrous 100 mg; 200 mg; 300 mg, respectively (10 mg/ml)
Reg. No.: 27/8.3/0151 27/8.3/0152 27/8.3/0153	

SCHEDULING STATUS:

S3

1 NAME OF THE MEDICINE:

LEUCOVORIN 100 mg/10 mL ABIC

LEUCOVORIN 200 mg/20 mL ABIC

LEUCOVORIN 300 mg/30 mL ABIC

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

LEUCOVORIN 100 mg/10 mL ABIC:

Each vial contains leucovorin calcium pentahydrate equivalent to 100 mg leucovorin (acid) anhydrous (10 mg/mL).

LEUCOVORIN 200 mg/20 mL ABIC:

Each vial contains leucovorin calcium pentahydrate equivalent to 200 mg leucovorin (acid) anhydrous (10 mg/mL).

LEUCOVORIN 300 mg/30 mL ABIC:

Each vial contains leucovorin calcium pentahydrate equivalent to 300 mg leucovorin (acid) anhydrous (10 mg/mL).

Excipients with known effect:

LEUCOVORIN 100 mg/10 mL ABIC contains 32,62 mg of sodium in each 10 mL vial.

LEUCOVORIN 200 mg/20 mL ABIC contains 65,24 mg of sodium in each 20 mL vial.

LEUCOVORIN 300 mg/30 mL ABIC contains 97,86 mg of sodium in each 30 mL vial.

For full list of excipients, refer to **section 6.1.**

3 PHARMACEUTICAL FORM:

Injection.

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.

4 CLINICAL PARTICULARS:

4.1 Therapeutic 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 anaemia due to folate deficiency.

4.2 Posology and method of administration:

Posology:

Megaloblastic anaemia secondary to folate deficiency:

A dosage of 1 to 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 x 10^{-6} M (24 hours after a 6 hour infusion)	10 to 15 mg/m^2 every 6 hours	48 to 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 to 30 hour post-infusion)		
Less than 1.5 x 10^{-6} M	10 to 15 mg/m^2 every 6 hours	48 hours
1.5 to 5 x 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 to 24 hours by intramuscular injection, bolus intravenous injection, or intravenous infusion in 0,9 % *m/v* sodium chloride solution, followed by 12 to 15 mg intramuscularly, or 15 mg orally, every six hours for the next 48 hours.

In general, it is recommended that administration of ABIC 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 ABIC LEUCOVORIN treatment also varies with the dosage of methotrexate and in patients with renal function impairment or pleural or peritoneal effusions.

Intravenous solutions containing ABIC LEUCOVORIN 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.

Paediatric population:

The safety and efficacy of ABIC LEUCOVORIN in children has not been established.

Method of administration:

For intravenous and intramuscular administration only.

For instructions on dilution of ABIC LEUCOVORIN before administration, refer to **section 6.6**.

4.3 Contraindications:

Hypersensitivity to leucovorin calcium or any of the excipients listed in **section 6.1**.

Leucovorin calcium should not be used as the sole anti-anaemic medicine 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.

4.4 Special warnings and precautions for use:

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.

Patients receiving ABIC LEUCOVORIN as a rescue from the toxic effects of methotrexate should be under the supervision of a doctor experienced in high-dose methotrexate therapy

Leucovorin, as contained in ABIC LEUCOVORIN, intensifies the toxicity of 5-fluorouracil. When these medicines 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 (refer to **section 4.5**). 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 (i.e., ABIC LEUCOVORIN) may increase the frequency of seizures in susceptible children by counteracting the anticonvulsant effects of barbiturates, hydantoin anticonvulsants and primidone (refer to **section 4.5**).

When used as a rescue from the effects of methotrexate, ABIC LEUCOVORIN should be used with caution in the presence of renal function impairment or pleural or peritoneal effusions, since such problems may affect the excretion of methotrexate.

ABIC LEUCOVORIN for injection and lyophilised powder for injection, when diluted with a diluent containing benzyl alcohol should not be used in premature or newborn infants.
ABIC LEUCOVORIN should never be given alone or in conjunction with inadequate amounts of hydroxy cobalamin for the treatment of pernicious anaemia.

Laboratory tests:

The following checks are important in patient monitoring when ABIC LEUCOVORIN 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 ABIC LEUCOVORIN 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.

Excipients:

LEUCOVORIN 100 mg/10 mL ABIC contains 32,62 mg of sodium in each 10 mL vial equivalent to 1,6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

LEUCOVORIN 200 mg/20 mL ABIC contains 65,24 mg of sodium in each 20 mL vial equivalent to 3,3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

LEUCOVORIN 300 mg/30 mL ABIC contains 97,86 mg of sodium in each 30 mL vial equivalent to 4,9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction:

ABIC LEUCOVORIN may increase the frequency of seizures in susceptible children by counteracting the anticonvulsant effects of barbiturates, hydantoin anticonvulsants and primidone (refer to **section 4.4**).

Concomitant administration of ABIC LEUCOVORIN with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (refer to **section 4.4**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The safety of ABIC LEUCOVORIN in pregnant women has not been established.

Breastfeeding:

The safety of ABIC LEUCOVORIN in breastfeeding has not been established. It is not known whether ABIC LEUCOVORIN is excreted into human breast milk.

Fertility:

No human data are available.

4.7 Effects on ability to drive and use machines:

ABIC LEUCOVORIN has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects:

Tabulated summary of adverse reactions:

Blood and lymphatic system disorders:	
Frequency unknown:	Thrombocytosis has been reported in patients receiving leucovorin (i.e., ABIC LEUCOVORIN) during intra-arterial infusion of methotrexate.
Immune system disorders:	
Frequency unknown:	Hypersensitivity reaction, including pyrexia, hives, itching, rash, wheezing.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/documents/adverse-drug-reactions-and-quality-problem-

reporting-form.

4.9 Overdose:

Refer to **section 4.8**. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 8.3 Erythropoietics (Haematinics)

ATC code: V03AF03

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.

5.2 Pharmacokinetic properties

Leucovorin readily crosses the blood brain barrier and is stored primarily in the liver.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection

6.2 Incompatibilities:

ABIC LEUCOVORIN must not be mixed with other medicines except those mentioned in **section 6.6**.

6.3 Shelf life:

24 months.

After dilution:

When diluted with 5 % glucose and 0,9 % sodium chloride, chemical and physical in-use stability has been demonstrated for 72 hours at room temperature under ambient light and 2 to 8 °C in dark.

6.4 Special precautions for storage:

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

Do not freeze.

For storage of ABIC LEUCOVORIN after dilution, refer to **section 6.3.**

6.5 Nature and contents of container:

LEUCOVORIN 100 mg/10 mL ABIC: a clear type I glass vial containing 10 mL of solution.

LEUCOVORIN 200 mg/20 mL ABIC: a clear type I glass vial containing 20 mL of solution.

LEUCOVORIN 300 mg/30 mL ABIC: a clear type I glass vial containing 30 mL of solution.

6.6 Special precautions for disposal and other handling:

For intravenous infusion, ABIC LEUCOVORIN may be diluted with 0,9 % *m/v* sodium chloride solution for

injection or 5 % glucose solution for injection before use (refer to **section 4.2**).

Prior to administration, ABIC LEUCOVORIN 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.

Any unused medicine or waste material should be disposed of in accordance with the local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand, Gauteng

South Africa, 2090

8 REGISTRATION NUMBER(S):

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

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

Date of registration: 28 August 2000.

10 DATE OF REVISION OF THE TEXT:

Teva Pharmaceuticals (Pty) Ltd.	**Product:** **Leucovorin 100 mg/10 ml; 200 mg/20 ml; 300 mg/30 ml Abic** **Dosage Form:** Vial **Strength:** Each vial contains leucovorin calcium pentahydrate equivalent to leucovorin (acid) anhydrous 100 mg; 200 mg; 300 mg, respectively (10 mg/ml)
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28 June 2024

LEUCOVORIN 100 mg/10 mL ABIC:

NAMIBIA: Reg. No./Nr.: 13/8.3/0127

NS2

BOTSWANA: Reg. No./Nr.: BOT1803297

S2

LEUCOVORIN 300 mg/30 mL ABIC:

NAMIBIA: Reg. No./Nr.: 13/8.3/0128

NS2

BOTSWANA: Reg. No./Nr.: BOT1803299

S2