Teva Pharmaceuticals (Pty) Ltd	**Product:** ABITREXATE 50/500/1 g/5 g Abitrexate 50 and Abitrexate 500: Each 1 ml contains methotrexate 25 mg. Abitrexate 1 g: Each 10 ml contains methotrexate 1 g. Abitrexate 5 g: Each 50 ml contains methotrexate 5 g.
	Date of Registration: 26 November 1986 **Approval date**: 08 July 2022

Approved Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ABITREXATE 50

ABITREXATE 500

ABITREXATE 1 g

ABITREXATE 5 g

Sugar free.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Abitrexate 50 and Abitrexate 500: Each 1 ml contains methotrexate 25 mg.

Abitrexate 1 g: Each 10 ml contains methotrexate 1 g.

Abitrexate 5 g: Each 50 ml contains methotrexate 5 g.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Abitrexate 50:

Clear, yellow-brown solution, free of visible particles.

Abitrexate 500:

Clear, yellow-brown solution, free of visible particles.

Abitrexate 1 g:

A clear orange to brown solution, free of visible particles.

Abitrexate 5 g:

A clear orange to brown solution, free of visible particles.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

- Lymphoblastic leukaemia in children and meningeal leukemia.
- Choriocarcinoma and related trophoblastic tumours of women.
- Women with non-metastatic trophoblastic disease, hydatidiform mole and chorioadenoma destruens.
- Carcinomas of the breast, tongue, pharynx and testes (in conjunction with chlorambucil and dactinomycin).
- Carcinoma of the lung and osteogenic sarcomas (high dose **ABITREXATE** with folinic acid rescue).
- Treatment of severe psoriasis (see **section 4.4**)
- Prevention of graft-versus-host reactions that result from marrow transplantation.
- Dermatomyositis, rheumatoid arthritis (not adequately responding to other therapy), Wegener's granulomatosis and pityriasis rubra pilaris.

4.2. Posology and method of administration:

Posology:

Lymphoblastic leukaemia: When used for induction, **ABITREXATE** in doses of 3,3 mg/m^2 in combination with prednisone 60 mg/m^2 given daily produced remission in 50 % of patients treated, usually within a period of 4 to 6 weeks. **ABITREXATE** alone or in combination with other medicines appears to be the medicine of choice for securing maintenance of medicine-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: **ABITREXATE** is administered twice weekly intramuscularly in doses of 30 mg/m^2. It has also been given in doses of 2,5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regime.

Meningeal leukaemia: Some patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may remain silent and be diagnosed only by examination of the cerebrospinal fluid which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of **ABITREXATE** from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the medicine is administered intrathecally. A common approach is to treat such patients as may actually manifest leukaemic involvement by direct intrathecal instillation of **ABITREXATE**.

Intrathecal administration: NOTE: For convenience, and to minimise the risk of overdosage, it is recommended that vials containing 50 mg of preservative-free **ABITREXATE**, be used for intrathecal administration. Administration is at intervals of 2 to 5 days and is usually repeated until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advised. Large doses may cause convulsions.

The following dosage regimen is based on age instead of body surface area:

Age (years)	Dose (mg)
< 1	6
1	8
2	10
3 or older	12

Similar doses are given prophylactically to patients with lymphoblastic leukaemia, often in association with cranial irradiation. **ABITREXATE** in intravenous doses of about 500 mg per m^2, followed by folinic acid rescue, may also produce effective concentrations in the CSF.

Choriocarcinoma and similar trophoblastic diseases: Doses of 15 to 30 mg daily intramuscularly for 5 days, at intervals of 1 to 2 weeks for 3 to 5 courses. Alternatively, 0,25 to 1 mg per kg body-weight up to a maximum of 60 mg has been given intramuscularly every 48 hours for 4 doses, followed by folinic acid rescue, and repeated at intervals of 7 days.

Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with **ABITREXATE** has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatiform mole. **ABITREXATE** administered in these disease states in doses similar to those recommended for choriocarcinoma.

Breast carcinoma: Prolonged cyclic combination chemotherapy with cyclophosphamide, **ABITREXATE** and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. **ABITREXATE** dosage was 40 mg/m^2 intravenously on the first and eighth days.

Combination chemotherapy may be necessary in patients with metastases.

A range of doses of **ABITREXATE** has been used in the management of solid tumours. Very high doses have been given by intravenous infusion, followed by folinic acid, in patients with osteogenic sarcoma and carcinoma of the lung and of the head and neck.

Psoriasis: ABITREXATE has been given intramuscularly, and intravenously in the treatment of psoriasis. Single weekly doses of 10 to 25 mg may be given by mouth or injection. Alternatively 2,5 mg has been administered by mouth every 12 hours for 3 doses or every 8 hours for 4 doses each week or 2,5 mg may be given daily by mouth for 5 days out of 7.

High-dose therapy: High dose therapy should be used only by qualified medical practitioners in

suitable hospital setting.

ABITREXATE RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF ABITREXATE:

CLINICAL SITUATION	LABORATORY FINDINGS	FOLINIC ACID DOSAGE AND DURATION
Normal **ABITREXATE** elimination.	Serum **ABITREXATE** level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	15 mg IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of **ABITREXATE** infusion).
Delayed Late **ABITREXATE** elimination.	Serum **ABITREXATE** level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 15 mg IM or IV every 6 hours, until **ABITREXATE** level is less than 0,05 micromolar.
Delayed Early **ABITREXATE** Elimination and/or Evidence of Acute	Serum **ABITREXATE** level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48	150 mg IV every 3 hours, until **ABITREXATE** level is less than 1

Renal Injury.	hours after adminstration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after **ABITREXATE** administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	micromolar; then 15 mg IV every 3 hours, until **ABITREXATE** level is less than 0,05 micromolar.

GUIDELINES FOR CALCIUM FOLINATE METHOTREXATE RESCUE DOSAGE AND ADMINISTRATION.

CLINICAL SITUATION	LABORATORY FINDINGS	LEVOFOLINIC ACID DOSAGE AND DURATION
Normal **ABITREXATE** elimination.	Serum **ABITREXATE** level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	7,5 mg IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of **ABITREXATE** infusion).
Delayed Late	Serum **ABITREXATE**	Continue 7,5 mg IM or

ABITREXATE elimination.	level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	IV every 6 hours, until **ABITREXATE** level is less than 0,05 micromolar.
Delayed Early **ABITREXATE** Elimination and/or Evidence of Acute Renal Injury.	Serum **ABITREXATE** level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after **ABITREXATE** administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	75 mg IV every 3 hours, until **ABITREXATE** level is less than 1 micromolar; then 7,5 mg IV every 3 hours, until **ABITREXATE** level is less than 0,05 micromolar.

Mycosis fungoides: Therapy with **ABITREXATE** appears to produce clinical remissions in half of the

cases treated. **ABITREXATE** has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

Rheumatoid arthritis: In case of intravenous or intramuscular administration of **ABITREXATE**, the starting dose in adults is 7,5 mg once weekly.

4.3. Contraindications:

- Hypersensitivity to methotrexate or any of the ingredients of **ABITREXATE**.
- Pregnancy and in lactation. (see **section 4.6**).
- Patients with psoriasis or rheumatoid arthritis with impaired renal or liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anaemia, and alcohol abuse.
- Interstitial pneumonitis associated with previous methotrexate therapy.
- Safety and efficacy in children have not been established other than in cancer chemotherapy.
- Active infections
- Immune-deficiency syndrome including HIV infection.
- Live attenuated vaccines.
- Concomitant use with sulphonamide containing medicines.

4.4. Special warnings and precautions for use:

Deaths have been reported with the use of **ABITREXATE** in the treatment of psoriasis and rheumatoid arthritis. In the treatment of psoriasis and rheumatoid arthritis, **ABITREXATE** should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or dermatological consultation.

- **ABITREXATE** should be administered under the supervision of a medical doctor experienced in the use of chemotherapeutic agents.

- **ABITREXATE** is an irritant; avoid contact with skin and mucous membranes.
- Severe, occasionally fatal, cutaneous or sensitivity reactions (e.g., toxic epidermic necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme, vasculitis and extensive herpetiform skin eruptions)may occur after the administration of methotrexate and recovery ensured mostly after discontinuation of the therapy.
- Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.
- During the use of **ABITREXATE** the following laboratory tests are generally advised: full blood counts and platelets; renal function tests and urine analysis; liver enzyme determination; bilirubin, serum albumin, chest X-ray is recommended. If clinically indicated, exclude tuberculosis and hepatitis.
- During the treatment of psoriasis and rheumatoid arthritis it is recommended to repeat those tests regularly: monthly haematology, every 1 – 3 months liver and kidney function.
- During antineoplastic treatment a more frequent control procedure is applied. On treatment initiation or a dose modification or during periods in which an enhanced risk on increased **ABITREXATE** blood levels (e.g. in case of dehydration) may develop, a more frequent monitoring is necessary.
- A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established (see **section 4.3**). Liver function tests abnormalities occur commonly after **ABITREXATE** administration andmay need therapy modification (see **section 4.3**). Treatment

should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced Impairment in liver function just prior to administration and/or serum albumin level decrease may indicate serious liver toxicity and require further examination (see **section 4.3**).

Due to its potentially toxic effect on the liver, additional hepatotoxic medicines should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see **section 4.5**). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicines concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicines.

- Lung function tests may be useful in case an **ABITREXATE** induced lung disease is suspected, in particular when initial base line values are available. **ABITREXATE** induced lung disease may occur at any moment. Pulmonary symptoms (in particular a dry, non-productive cough and fever) require immediate treatment discontinuation and thorough examination. In the treatment of **ABITREXATE** induced (interstitial) pneumonitis after immediate discontinuation of therapy, corticosteroid treatment is indicated. In case of the occurrence of lung toxicity re-initiation of therapy is contraindicated.

  In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis
- **ABITREXATE** should be used with extreme care in patients with infection, peptic ulcer, ulcerative colitis, debility and in the very young or aged.
- When vomiting, diarrhoea, or stomatitis occurs, with possible dehydration,

ABITREXATE treatment should be discontinued until recovery

- Diarrhoea and ulcerative stomatitis require discontinuation of treatment because of the risk of haemorrhagic enteritis and fatal intestinal perforation.
- In case of severe leucopenia occurring during treatment, there is a high risk of bacterial infections. When infection occurs, discontinuation of **ABITREXATE** and adequate antibacterial therapy is indicated. In case of severe bone marrow depression blood or thrombocytes transfusion may be necessary.
- Renal function should be monitored by renal function tests and urine analysis. As **ABITREXATE** is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects. Patients with decreased renal function should be monitored more frequently as **ABITREXATE** elimination time is increased in renal dysfunction (see **section 4.3**). This particularly applies to the co-administration of medicines which affect methotrexate excretion, cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorders. Dehydration may also potentiate the toxicity of methotrexate. Alkalising the urine and increase a high diuresis is recommended, especially in high dose treatment. At the onset of nephrotoxicity also immediate discontinuation of therapy is indicated.
- During **ABITREXATE** therapy and until at least six months after treatment with **ABITREXATE**, contraceptive precautions should be taken by female as well as male patients.
- The data on the carcinogenicity risk in case of use of **ABITREXATE** by rheumatoid arthritis patients are limited.
- Patients should be fully informed on the risks of **ABITREXATE** therapy and should be instructed to report any manifestation of toxicity immediately.
- It is recommended to carry out a liver biopsy in patients with psoriasis and rheumatoid arthritis. Fibrosis of intermediate revering or any cirrhosis requires discontinuation of therapy.

- The combined administration of **ABITREXATE** and other potentially hepatotoxic medicines and alcohol should be avoided.
- Lymphomas may develop in patients treated with low dose **ABITREXATE.** Spontaneous remission may occur when **ABITREXATE** therapy is stopped; therefore, treatment with oncolytics is not necessarily indicated. First, it is necessary to stop **ABITREXATE** treatment when this adverse event occurs. If remission fails to appear, an adequate treatment has to be started.
- **ABITREXATE** is contraindicated in patients with hepatic or renal impairment. It should be used cautiously in alcoholics or those with ulcerative disorders of the gastro-intestinal tract. With high-dose regimens, plasma concentrations of **ABITREXATE** and urinary excretion should be monitored.

  Precipitation of **ABITREXATE** or its metabolites in the renal tubules may be prevented by alkalinisation of the urine using sodium bicarbonate, maintaining an adequate urine flow, and the withholding of therapy until pleural or ascitic effusions, which may act as a depot for methotrexate, have been drained.

  It is essential that examinations of blood and tests of renal and liver function should be made before, during and after each course of treatment with **ABITREXATE.** If there is a severe fall in the white cell or platelet counts, **ABITREXATE** should be withdrawn.
- Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of **ABITREXATE**.
- Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population
- Due to risk of phototoxicity patients must avoid sunlight and solarium.
- During high dose treatment, folinic acid should be given concomitantly. The serum concentration of methotrexate is a valuable indicator for how long the folinic acid treatment should be continued. Forty eight hours after the start of the **ABITREXATE** infusion, the residual methotrexate-level

should be measured. If the residual methotrexate-level is < 0,5µmol/l, no additional treatment with folinic acid is necessary.

- Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.
- *Fertility:*

  Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.
- *Teratogenicity – Reproductive risk*

  Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age.

4.5. Interaction with other medicines and other forms of interaction:

ABITRTEXATE is normally used in combination with other cytostatics. Additive toxicity can be expected during combination chemotherapy with medicines with the same pharmacological effect, especially regarding bone marrow inhibition, renal, gastrointestinal and pulmonary toxicity (see **section 4.4**).

- The effects of **ABITREXATE** may be enhanced by concurrent administration of chloramphenicol, phenytoin, probenecid, salicylates, sulphonamides, doxorubicin, bleomycin, cyclophosphamide, aminoglycosides, allopurinol, vincristine, hydrocortisone, prednisone, asparaginase, cytosine arabinoside and tetracyclines.

- Non-steroidal anti-inflammatory drugs (NSAIDS), salicylates and other weak organic acids, like probenecid, can lower tubular secretion of **ABITREXATE** resulting in increased toxicity. Use of **ABITREXATE** with these medicines should be made carefully under strict supervision. The potential toxicity of **ABITREXATE** is increased when diuretics are also used. In rheumatology, a combination therapy of low-dose **ABITREXATE** and a NSAID is commonly used. Care should be taken in combining high dose **ABITREXATE** with potentially nephrotoxic therapy (e.g. cisplatin).
- Regular alcohol consumption and administration of additional hepatotoxic medicines increase the probability of hepatotoxic effects of methotrexate.
- Patients taking potentially hepatotoxic medicines during **ABITREXATE** therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity.
- Be aware of pharmacokinetic interactions between methotrexate, anticonvulsant medicines (reduced methotrexate blood levels), and 5-flourouracil (increased $t_{1/2}$ of 5-flourouracil).
- Antibiotics, like penicillin's, glycopeptides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.
- Interaction with therapeutic radiation may occur. In combination with other cytostatic medicines pharmacodynamic interactions may occur; resulting in increased therapeutic activity and increased toxicity.
- No vaccination with live virus vaccines should be performed in patients receiving **ABITREXATE.** Partial or total protection can be obtained through inactivated vaccines.
- In some cases a potentiation of bone marrow suppression in patients treated with **ABITREXATE** by trimethoprim/sulphamethoxazole has been reported, probably by additional folic acid antagonism. The combined use of **ABITREXATE** and sulphonamides should not occur.
- Vitamin preparations containing folic acid or folic acid derivatives may decrease the effect of

systemically administered **ABITREXATE**. Preliminary human and animal studies have shown that after intravenous administration of calcium folinate a small amount penetrates into the cerebrospinal fluid, predominantly as 5-methyltetrahydrofolate, and this amount is a factor 1 to 3 lower than the normal **ABITREXATE** concentration after intrathecal administration. Nevertheless high doses of calcium folinate may lower the effectivity of intrathecally administered **ABITREXATE**. Folate deficiencies may increase **ABITREXATE** toxicity.

- Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.
- Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored under concomitant methotrexate administration.
- Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing beverages, black tea) should be avoided during methotrexate therapy, since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.
- The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, and stomatitis and neurotoxicity with intrathecal administration. Whilst this effect can be reduced by administering calcium folinate, the concomitant use should be avoided.

4.6. Fertility, pregnancy and lactation:

ABITREXATE must not be used during pregnancy and lactation. Effective contraception must be used during treatment with methotrexate and at least 6 months thereafter. Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a

pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

See **section 4.3** and s**ection 4.8** (Urogenital and Other disorders)

Pregnancy:

Methotrexate is contraindicated during pregnancy (see **section 4.3**). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.

Breastfeeding:

As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see **section 4.3**). If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

Fertility:

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

4.7 Effects on ability to drive and use machines:

Central nervous symptoms such as fatigue and drowsiness can occur during treatment, methotrexate has minor or moderate influence on the ability to drive and use machines

4.8 Undesirable effects:

In general the incidence and severity of acute side effects is related to the dosage and frequency of administration.

Infections and infestations:

Frequent: Feeling unwell, chills, fever, increased risk for infection

Less frequent: Opportunistic infections, sepsis, infections caused by the cytomegaly virus.

Neoplasms benign and malignant (including cysts and polyps):

Less frequent: Lymphomas.

Blood and the lymphatic system disorders:

Frequent: **ABITREXATE** may suppress haematopoiesis and cause anaemia, leukopenia and/or thrombocytopenia. In patients with existing haematopoietic insufficiencies **ABITREXATE** should not be used.

In psoriasis and rheumatoid arthritis treatment should be discontinued immediately in case of a significant drop in the blood count. In the treatment of neoplasia, **ABITREXATE** may only be continued if the possible cure justifies the risk of serious myelosuppression. Myelosuppression may also occur after intrathecal administration of **ABITREXATE**. Patients with serious granulocytopenia and fever should undergo immediate evaluation and usually require parenteral broad-spectrum antibiotics. Pancytopenia has been reported.

Less frequent: Megaloblastic anaemia, aplastic anaemia, lymphadenopathy, neutropenia and eosinophilia, agranulocytosis, bone marrow depression, lymphoproliferative disorders (partly reversible).

Immune system disorders:

Less frequent: Immunosuppression.

ABITREXATE should not be used in case of active infection (see **section 4.3**).

Metabolism and nutrition disorders:

Less frequent: Diabetes.

Psychiatric disorders:

Less frequent: Insomnia.

Nervous system disorders:

Frequent: Headache, drowsiness, fatigue.

Less frequent: Vertigo, confusion, depression, severely impaired vision, mood alterations, pain, muscular asthenia or paraesthesia of the extremities, change in sense of taste (metallic taste), meningism (paralyses, vomiting), acute aseptic meningitis, aphasia, hemiparesis, paresis, and convulsions.

There are reports of leukoencephalopathy after intravenous administration of **ABITREXATE** to patients who underwent craniospinal irradiation.

Chronic leukoencephalopathy was also reported in patients with osteosarcoma who were administered **ABITREXATE** with calcium folinate rescue therapy, even without cranial irradiation.

Discontinuation of **ABITREXATE** does not always result in complete recovery.

A transient acute neurological syndrome has been observed in patients who underwent **ABITREXATE** treatment. The clinical manifestations may consist of abnormal behaviour, focal sensomotoric phenomena, and abnormal reflexes. The exact cause of these symptoms is unknown.

After intrathecal administration of **ABITREXATE**, the possible toxic side effects pertaining to the central nervous system may be classified in the following way:

- chemical arachnoiditis with symptoms such as headache, backache, neck stiffness and fever
- paresis
- leukoencephalopathy with confusion, agitation, somnolence, ataxia, dementia and convulsions.

Neurotoxic reactions are especially associated with the intrathecal use of **ABITREXATE**.

Eye disorders:

Less frequent: Visual disturbance, conjunctivitis, retinopathy.

Ear and labyrinth disorders:

Frequent: Dizziness.

Cardiac disorders:

Less frequent: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders:

Less frequent: Vasculitis, hypotension, thromboembolic event (including arterial thrombosis, cerebral thrombosis, thrombophlebitis, deep vein thrombosis and pulmonary embolism).

Respiratory, thoracic and mediastinal disorders:

Less frequent: Interstitial pneumonitis which may be fatal, and interstitial obstructive lung disease may occur.

Pulmonary symptoms (in particular a dry, non-productive cough) or a non-specific pneumonitis during the **ABITREXATE** treatment may indicate a potentially dangerous lesion and requires immediate discontinuation of the treatment and a thorough examination. Although symptoms may be varying, a patient with **ABITREXATE** induced lung disease typically shows fever, cough, dyspnoea, hypoxemia and infiltration in lung radiography. An infection should be excluded.

This condition may occur at any dosage. **ABITREXATE** related lung pathology may also occur after intrathecal administration of **ABITREXATE**. At the onset of **ABITREXATE** induced lung disease, the re-administration of **ABITREXATE** is contraindicated.

Pulmonary fibrosis, pharyngitis, apnoea, bronchial asthma, Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed; pleural effusion.

Gastrointestinal disorders:

Frequent: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhoea, haematemesis, melena, ulcerative stomatitis (especially during the first 24-48 hours after administration of methotrexate),enteri gastrointestinal ulceration and bleeding, enteritis and perforations, dyspepsia

Less frequent: Malabsorption, toxic megacolon.

Hepato-biliary disorders:

Frequent: Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin)

Less frequent: Acute hepatitis, reactivation of chronic hepatitis, acute liver degeneration; furthermore, herpes simplex hepatitis and liver insufficiency have been observed

ABITREXATE may cause acute increase in transaminases or chronic fibrosis and cirrhosis. Chronic toxicity is potentially lethal. It usually occurs after chronic use (mostly 2 years or longer) and after a total dose of at least 1,5 g.

Hepatotoxicity appeared to be determined by the total cumulative dose. The effect is potentiated by alcoholism, obesity, diabetes and advanced age.

Information on progression and reversibility of lesions is not available. Care should be taken in the presence of existing liver damage or decreased liver function.

Liver function tests, including serum albumin should be carried out regularly prior to administration.

Liver function test may be normal in cases of fibrosis and cirrhosis. These conditions can only be diagnosed by biopsy.

In case of psoriasis and rheumatoid arthritis it is recommended to perform a liver biopsy after a total cumulative dose of 1,5 g. Intermediate fibrosis or any cirrhosis usually prompts discontinuation of the therapy.

Skin and subcutaneous tissue disorders:

Frequent: Exanthema, erythema, itching.

Less frequent: Pruritus, urticaria, photosensitivity, depigmentation, alopecia, ecchymosis, telangiectasia, acne, furunculosis, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, increased pigmentary changes of nails, petechiae, erythema multiforme, cutaneous erythematous eruptions, acute paronychia, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported; allergic vasculitis, hidradenitis.

Psoriatric lesions may worsen by exposure to UV-radiation. Radiation dermatitis and sunburn may flare up by **ABITREXATE** administration.

Toxic epidermal necrolysis and Stevens Johnson syndrome.

Frequency unknown: Skin exfoliation/dermatitis exfoliative

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia/myalgia, osteoporosis, stress fracture.

A sudden increase in the number of rheumatoid nodules has been reported in patients with rheumatoid arthritis.

Frequency unknown: Osteonecrosis of jaw (secondary to lymphoproliferative disorders)

Renal and urinary disorders:

Frequent: Serious nephropathy or renal insufficiency, uraemia, cystitis and haematuria.

ABITREXATE may cause renal toxicity with acute renal insufficiency. Nephrotoxicity may be caused by the deposition of **ABITREXATE** and 7-hydroxymethotrexate in the renal tubuli.

Less frequent: Renal failure, oliguria, anuria, proteinuria

Pregnancy, puerperium and perinatal conditions:

Frequent: Foetal abnormalities, abortion.

Teratogenic effects and foetal deaths.

Reproductive system and breast disorders:

Frequent: Defective oogenesis or spermatogenesis, transient oligospermia,

menstrual dysfunction and vaginal discharge, infertility, suppression of spermatogenesis, loss of libido, and impotence.

Less frequent: inflammation and ulceration of the vagina

General disorders and administrative site conditions:

Frequent: Inexplicable fatigue

Less frequent: Severe allergic reactions progressing to anaphylactic shock, fever, impaired wound healing.

Incidental cases of anaphylactic reactions have been reported.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reactions Reporting Form'**, found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms of overdose:

Toxicity of **ABITREXATE** mainly affects the haematopoietic and gastrointestinal systems.

Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.

There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

Therapeutic measures in case of overdose:

Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of **ABITREXATE**.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10-7 mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor

peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION:

Methotrexate is an antineoplastic medicine, which acts as an antimetabolite of folic acid. It also has immunosuppressant qualities.

5.2. Pharmacokinetic properties:

It is distributed mainly in the extracellular spaces but a proportion penetrates cell membranes and is strongly bound to dihydrofolate reductase. Only small amounts of methotrexate diffuse into the cerebrospinal fluid but higher concentrations are achieved with high doses. About 50 % is bound to plasma proteins. Biphasic and triphasic clearance from plasma has been reported. The majority of a dose is excreted unchanged in the urine within 24 hours and up to 15 % may appear in the bile although because of re-absorption less may be excreted in the faeces. Bound methotrexate may be retained in the body for many months.

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients:

The other ingredients in **ABITREXATE** are:

Sodium hydroxide, hydrochloric acid, water for injection

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

Store in original packaging:

30 months

Shelf-life after reconstitution and/or first opening of the product:

24 hours

6.4. Special precautions for storage:

Store at or below 25 ºC and protect from light.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN

6.5. Nature and contents of container:

Abitrexate 50: Single 2 ml vial

Abitrexate 500: Single 20 ml vial

Abitrexate 1 g: Single 10 ml vial.

Abitrexate 5 g: Single 50 ml vial.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

While preparing **ABITREXATE** injections protective gloves, a mask and safety goggles should be worn.

The preparation of **ABITREXATE** has to take place in a vertical laminar air flow hood. Spillage of **ABITREXATE** should be washed with a copious amount of water .

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West, Waterfall City

Midrand, Gauteng,

South Africa

8. REGISTRATION NUMBER:

Abitrexate 50: T/26/63

Abitrexate 500: T/26/64

Abitrexate 1 g: T/26/57

Abitrexate 5 g: W/26/386

9. DATE OF FIRST AUTHORISATION:

26 November 1986

10. DATE OF REVISION OF TEXT:

08 July 2022