Teva Pharmaceuticals (Pty) Ltd.	**Product:** Abitrexate 2,5 mg Tablets **Dosage Form:** Tablets **Strength:** 2,5 mg methotrexate as the sodium salt
Reg. No.: 37/26/0466	

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ABITREXATE 2,5 mg TABLETS

ABITREXATE 10 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABITREXATE 2,5 mg TABLETS: Tablets contain 2,5 mg of methotrexate as the sodium salt.

ABITREXATE 10 mg (Tablets): Tablets contain 10 mg of methotrexate as the sodium salt.

Contains sugar (lactose monohydrate, 77,758 mg per 2,5 mg tablet and 150,032 mg per 100 mg tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ABITREXATE 2,5 mg TABLETS are flat-faced, yellow, bevel-edged and scored with a diameter of 6,5 mm, code MTX2 ½ on one side, PCH on the other side.

ABITREXATE 10 mg tablets are flat-faced, yellow, bevel-edged and scored with a diameter of 9 mm code MTX10 on one side.

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

Important warning about the dosage of ABITREXATE:

In the treatment of psoriasis and rheumatoid arthritis requiring dosing once a week, ABITREXATE must only be taken once a week. Dosage errors in the use of ABITREXATE can result in serious adverse reactions, including death. Please read this section of the professional information very carefully.

Indications requiring dosing once a week: Psoriasis and rheumatoid arthritis:

The prescriber should specify the day of intake on the prescription.

ABITREXATE may be given by mouth. The dose of ABITREXATE, the dosage frequency, the total dose and combination with other cytostatic medicine and/or folinic acid are subject to frequent modification as scientific knowledge improves.

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 appear 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 either by mouth or 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 installation 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 flowing 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/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 by mouth or 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 hydatidiform 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 the head and neck.

Psoriasis:

See Box Warning above

ABITREXATE has been given by mouth, 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 specialists in a 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	15 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of ABITREXATE infusion).

	micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	
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 PO, IM or 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).	150 mg IV every 3 hours, until ABITREXATE level is less than 1 micromolar; then 15 mg IV every 3 hours, until ABITREXATE level is less than 0,05 micromolar.

GUIDELINES FOR ISOVORIN* 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	7,5 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of ABITREXATE infusion).

	than 0,2 micromolar at 72 hours.	
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 7,5 mg PO, IM or 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. Dosage is usually 2,5 to 10 mg daily by mouth for weeks or months. Dose levels of medicine and adjustment of dose regime by reduction or cessation of medicine are guided by patient response and haematologic monitoring. ABITREXATE has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

Rheumatoid arthritis:

See Box Warning above

In case of oral administration of ABITREXATE, initially 2,5 mg to 5 mg every 12 hours for 3 doses once a week the dosage being increased as necessary in increments of 2,5 mg per week up to a maximum of 20 mg per week or initially 10 mg once a week, the dosage being increased as necessary up to 20 mg per week.

4.3 Contraindications

- Hypersensitivity to methotrexate or to any of the ingredients of ABITREXATE listed in section 6.
- ABITREXATE is contraindicated in pregnancy and lactation. (see section 4.6).
- ABITREXATE is contraindicated in patients with psoriasis or rheumatoid arthritis with serious renal or liver disorders, bone marrow hypoplasia, openia, thrombocytopenia, anaemia, and alcohol abuse.
- Safety and efficacy in children have not been established other than in cancer chemotherapy.
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis.
- Active infectious disease.
- Severe acute or chronic infections and immunodeficiency syndrome.
- During ABITREXATE therapy concurrent vaccination with live vaccines must not be carried out.
- ABITREXATE tablets should not be used concomitantly with medicines with antifolate properties (see section 4.5).

4.4 Special warnings and precautions for use

ABITREXATE should be administered under the close supervision of a medical doctor experienced in the use of chemotherapeutic medicines.

Use in psoriasis and in rheumatoid arthritis (RA):

ABITREXATE is an irritant; avoid contact with skin and mucous membranes.

While in general a low dose of ABITREXATE is applied in the treatment of psoriasis and rheumatoid arthritis, as compared to the doses used in antineoplastic therapy, intoxication and death may occur.

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.

The patient should be clearly informed that, in cases of psoriasis and rheumatoid arthritis, ABITREXATE is taken once weekly (see section 4.2).

The prescriber may specify the day of intake on the prescription.

Patients should be aware of the importance of adhering to once weekly intakes which is that daily/more frequent administration can result in severe toxicity.

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 psoriasis and rheumatoid arthritis patients after a total cumulative dose of 1,5 g. Fibrosis of intermediate revering or any cirrhosis usually requires discontinuation of therapy. Although mild changes usually are no reason to avoid or discontinue therapy, ABITREXATE should be used with care in patients.

Lung manifestations of rheumatoid arthritis and other connective tissue disorders are recognised to occur. In patients with rheumatoid arthritis, the medical practitioner should be specifically alerted to the potential for methotrexate induced adverse effects on the pulmonary system.

Nervous system:

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

Neurotoxic reactions are especially associated with the intrathecal use of methotrexate.

Chronic oencephalopathy was also reported in patients with osteosarcoma who were administered high dosages of ABITREXATE with calcium folinate rescue therapy, even without cranial irradiation. Discontinuation of ABITREXATE treatment does not always result in complete recovery.

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

Monitoring (prior to starting treatment):

Before beginning or reinstituting ABITREXATE after a rest period, the patient's renal, liver and bone marrow function should be assessed by history, physical examination and laboratory tests. A chest X-ray should also be taken (see Respiratory effects below).

Monitoring (during and after treatment):

During the use of ABITREXATE the following laboratory tests are generally advised: hemograms, counting of the platelets and haematocrit; renal function tests and urine analysis; liver enzyme determination; chest X-ray is recommended. During the treatment of psoriasis, it is recommended to repeat these tests regularly: monthly haematology, every 1 to 3 months for liver and kidney function.

Usually during antineoplastic treatment, a more frequent control procedure is applied. On treatment initiation or a dose modification or during periods with an enhanced risk on increased methotrexate blood levels (e.g. in case of dehydration), a more frequent control is to be done.

Haematopoietic suppression is common and may occur without warning when a patient is on an apparently "safe" dose, so full blood counts should be closely monitored during and after treatment. In patients with existing haematopoietic insufficiencies ABITREXATE should be used with care, or not at all. If any clinically significant drop in blood cell count occurs, ABITREXATE should be stopped immediately, and appropriate therapy instituted. Patients should be advised to report all signs and symptoms suggestive of infection or of a blood dyscrasia.

Other warnings/precautions:

Pleural effusions and ascites should be drained before ABITREXATE is started. Methotrexate can accumulate in these fluids and may be re-excreted into the circulation, prolonging the serum half-life and resulting in unexpected toxicity (e.g. myelosuppression – see below)

ABITREXATE should be used with extreme caution in debility, extreme youth, old age and psychiatric disorders.

Adequate hydration prior to and during treatment is required to limit the risk of renal toxicity (see below).

Folate deficiency may increase methotrexate toxicity.

Systemic toxicity may follow intrathecal use (appropriate monitoring required).

Tumour lysis syndrome may occur in patients with rapidly growing tumours.

If acute methotrexate toxicity occurs patients may require folinic acid (to neutralise bone marrow effects). Plasma methotrexate levels should be monitored in order to calculate the appropriate dose.

Patients should report all symptoms and signs suggestive of infection, especially sore throat.

Diabetic patients who are treated with insulin have increased risk for liver toxicity.

Hepatotoxicity:

ABITREXATE may cause hepatotoxicity, chronic liver fibrosis, and cirrhosis but generally only after prolonged use (mostly 2 years or longer). Chronic toxicity is potentially lethal. A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient deviation in liver function tests has often been observed after ABITREXATE administration and usually do not lead to therapy modification. Impairment in liver function just prior to administration and/or serum albumin level decreased may indicate serious liver toxicity and require further examination.

Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 - 20 %, however ABITREXATE should not be started or should be discontinued if there are any clinically relevant abnormalities of liver function tests or liver biopsy. If such abnormalities return to normal within two weeks, the medical practitioner may consider it appropriate to re-start ABITREXATE.

Test results are often normal in cases of fibrosis and cirrhosis. These conditions can only be diagnosed by biopsy.

The combined administration of ABITREXATE and other potentially hepatotoxic medicines and alcohol should be avoided.

In studies with psoriasis patients, hepatotoxicity appeared to be determined by the total cumulative dose. The effect is potentiated by:

- Daily (rather than weekly) dosing
- History of alcohol abuse
- History of liver disease including hepatitis B or C
- Family history of hereditary hepatopathy

Other factors that may indicate an increased risk include:

- Diabetes mellitus
- Adiposity
- History of exposure to hepatotoxic medicines or chemicals.

Liver biopsies:

Liver biopsies should be considered after cumulative doses > 1,0 to 1,5 g, if hepatic impairment is suspected.

In patients with risk factors (see above), liver biopsy is recommended during or shortly after starting ABITREXATE.

Since a small percentage of patients discontinue therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase (i.e. when longer-term therapy is proposed).

In low risk patients with RA, there is no robust evidence to support use of a liver biopsy to monitor hepatic toxicity (see above).

In case of longer-term treatment of psoriasis with ABITREXATE, liver biopsies should be performed.

Haematological effects (myelosuppression):

ABITREXATE can suppress haematopoiesis. This can occur abruptly and with apparently “safe” doses. Monitoring is therefore required (see above).

ABITREXATE may suppress haematopoiesis and cause anaemia, openia and/or thrombocytopenia. In patients with existing haematopoietic insufficiencies ABITREXATE should be used with care, or not at all.

If there are clinically significant falls in white cell or platelet counts, ABITREXATE should be stopped immediately.

Respiratory effects:

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 is a potentially dangerous condition which may occur at any moment during therapy with dosages higher than 7,5 mg weekly. The condition is not always completely reversible. Pulmonary symptoms (in particular a dry, non-productive cough), dyspnoea, fever, hypoxemia and infiltration in lung radiography may require treatment interruption and thorough examination. An infection should be excluded. In the treatment of ABITREXATE induced (interstitial) pneumonitis after immediate discontinuation of therapy, corticosteroid treatment is indicated. In case of occurrence of lung toxicity re-initiation of therapy is contraindicated.

Patients should be informed of the risk, monitored for relevant symptoms at every visit and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

If interstitial fibrosis develops it may be treatment-resistant.

In addition, pulmonary alveolar haemorrhage has been reported with ABITREXATE 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.

Gastrointestinal effects:

ABITREXATE should be used with extreme care in patients with infection, peptic ulcer, ulcerative colitis, debility and in the very young or aged.

Diarrhoea and ulcerative stomatitis require discontinuation of treatment because of the risk of haemorrhagic enteritis and death by intestinal perforation.

Following the occurrence of haematemesis, black coloured stools or blood in the stools, treatment must be discontinued.

When vomiting, diarrhoea, or stomatitis occurs, with possible dehydration, ABITREXATE treatment should be discontinued until recovery.

In addition, other conditions leading to dehydration such as emesis, can increase the toxicity of methotrexate due to elevated levels of the active substance. In these cases, use of ABITREXATE should be interrupted until symptoms cease. It is important to determine any increase in active substance levels within 48 hours of therapy, otherwise irreversible methotrexate toxicity may occur.

Immunosuppressive activity:

The immunosuppressive effect of ABITREXATE should be taken into account when immune responses of patients are important or essential. Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.

In case of severe openia occurring during treatment bacterial infections could set in. When infection occurs, discontinuation of ABITREXATE and adequate antibacterial therapy is indicated.

Patients with serious granulocytopenia and fever should undergo immediate examination and usually require parenteral broad-spectrum antibiotics.

In case of severe bone marrow depression blood or thrombocytes transfusion may be necessary.

Responses to concurrent vaccination may be decreased, as ABITREXATE has some immunosuppressive activity. Vaccination with live vaccines are contraindicated during ABITREXATE therapy as severe antigenic reactions may occur (see section 4.3).

Renal effects:

Special care should be taken in the patients with decreased renal function, and with reduced doses, as the ABITREXATE elimination time is increase in renal dysfunction.

High dosages of ABITREXATE may cause renal toxicity and acute renal insufficiency. Nephrotoxicity is usually caused by the deposition of ABITREXATE and 7-hydroxymethotrexate in the renal tubuli.

At the onset of nephrotoxicity also immediate discontinuation of therapy is indicated.

Renal lesions may develop if the urinary flow is impeded and urinary pH is low, especially if large doses have been administered.

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 deport for methotrexate, have been drained.

As methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions.

If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicines that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly.

If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate.

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment.

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.

*Effects on fertility and reproduction (*see section 4.6*)*:

During ABITREXATE therapy and until at least three months after treatment with ABITREXATE contraceptive precautions should be taken by both female and male patients.

Thus far there are no indications for an increased risk of carcinogenicity in humans undergoing prolonged therapy, such as psoriasis patients. The data on the carcinogenicity risk in case of use of ABITREXATE by rheumatoid arthritis patients are limited.

Fertility:

Methotrexate, contained in ABITREXATE 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, contained in ABITREXATE 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. In non-oncologic indications, the absence of pregnancy must be confirmed before ABITREXATE is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men (see section 4.6).

Development of malignant lymphomas:

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 should be used with great care in patients with hepatic or renal impairment. It should also be used cautiously in alcoholics or those with ulcerative disorders of the gastrointestinal tract.

Since cases of encephalopathy/ leukoencephalopathy have occurred in cancer patients treated with methotrexate (e.g. ABITREXATE), this cannot be ruled out either for patients with non-cancer indications.

The disappearance of methotrexate from plasma should be monitored, if possible. This is recommended in particular when high, or very high doses are administered in order to permit calculation of an adequate dose of ovorin (folinic acid) rescue.

ABITREXATE given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

The interactions of ABITREXATE and other antirheumatic medicines such as gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic medicines have not been studied comprehensively, and concurrent use may increase the incidence of adverse reactions.

Concomitant administration of folate antagonists such as trimethoprim/sulfamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

It is recommended to check levels of vitamin B12 prior to initiating folic acid supplementation, particularly in adults aged over 50 years, as folic acid intake may mask a vitamin B12 deficiency.

Methotrexate may cause adverse urinary tract reactions, such as cystitis and haematuria.

Serious skin reactions:

Severe (occasionally fatal) skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported within a few days of a single or multiple dose of ABITREXATE (see section 4.8).

When concurrent administration of ABITREXATE and radiotherapy takes place, there can be an increased risk of necrosis of soft tissue.

Medicines given concomitantly (see section 4.5).

Periodic evaluation by specific cognitive tests to detect early signs of cognitive impairment is advised in children.

ABITREXATE contains lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take ABITREXATE.

4.5 Interaction with other medicines and other forms of interaction

Concurrent use contraindicated:

No vaccination with live virus vaccines should be performed in patients receiving ABITREXATE (see section 4.3). Partial or total protection can be obtained through inactivated vaccines.

Avoid concomitant use:

In some cases, a potentiation of the 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 is therefore strongly advised against.

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis and neurotoxicity with intrathecal administration. Whilst this

effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

Colestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation.

Antipsychotics – increased risk of agranulocytosis with olanzapine.

Retinoids – plasma concentrations of methotrexate increased by acitretin – also increased risk of hepatotoxicity.

Non-steroidal anti-inflammatory drugs (NSAIDS) should not be administered prior to or simultaneously with high dose ABITREXATE treatment (>10 mg methotrexate per week).
Increased serum levels of ABITREXATE have been reported at simultaneous administration of some NSAIDS with high dose ABITREXATE resulting in death by serious haematologic or gastrointestinal toxicity.
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 in particular at simultaneous use of NSAIDS when also diuretics are used. In rheumatology, a combination therapy of low-dose ABITREXATE and NSAID is commonly used.

The effects of ABITREXATE may be enhanced by concurrent administration of diphenylhydantoins, acidic anti-inflammatory medicines, aminobenzoic acid, chloramphenicol, phenylbutazone, phenytoin, probenecid, salicylates, sulphonamides, tranquilisers, oral contraceptives, amidopyrine derivatives, thiazide diuretics, oral hypoglycaemics, probenecid, or sulfinpyrazone, oral hypoglycaemics, doxorubicin, bleomycin, cyclophosphamide, aminoglycosides, allopurinol, vincristine, hydrocortisone, prednisone, asparaginase, cytosine arabinoside and tetracyclines.

Caution required:

Care should be taken in combining high dose ABITREXATE with potentially nephrotoxic therapy (e.g. cisplatin).

Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may influence the intestinal flora and inhibit ABITREXATE (re) absorption.

Ciprofloxacin – excretion of methotrexate possibly reduced (increased risk of toxicity).

Penicillin – reduced excretion of methotrexate - increased risk of toxicity (haematological and gastrointestinal).

Antiepileptics:

Antifolate effect of methotrexate increased by phenytoin

Phenytoin – absorption possible decreased by cytotoxics (risk of exacerbation of convulsions)

Enzyme-inducing antiepileptics – increased/altered metabolism and/or clearance of methotrexate

Carbamazepine, phenytoin and valproate serum levels can be reduced by antineoplastic medicines with seizures if the antiepileptic doses are not raised appropriately.

Pyrimethamine – increased anti-folate effect of ABITREXATE.

Digoxin absorption decreased by cytotoxics as contained in ABITREXATE.

Ciclosporin - increased risk of toxicity.

Interaction with therapeutic radiation may occur and can increase the risk of soft tissue or bone necrosis.

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment or renal function.

Methotrexate increases plasma levels of mercaptopurine. Combinations of methotrexate and mercaptopurine may therefore require dose adjustment.

In combination with other cytostatic medicines pharmacodynamic interactions may occur; resulting in increased therapeutic activity and increased toxicity.

Immunosuppressant, leflunomide – risk of toxicity.

Theophylline - ABITREXATE possibly increases plasma concentrations of theophylline. Excessive consumption of beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, 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.

Administration of additional haematotoxic medicines (e.g. metamizole) increases the probability of severe haematoxic effects of ABITREXATE.

Omeprazole and pantoprazole – excretion of ABITREXATE possibly reduced (increased risk of toxicity).

One should be aware of pharmacokinetic interactions between methotrexate, anticonvulsant medicines (reduced methotrexate blood levels), and 5-fluorouracil (increased t½ of 5--fluorouracil).

Acitretin (a treatment for psoriasis) is metabolised to eretinate. ABITREXATE levels may be increased by eretinate and severe hepatitis has been reported following concomitant use.

Triamterene - bone marrow suppression and reduced folate concentrations have been reported when triamterene and ABITREXATE were co-administered.

Hepatic, haematotoxic and nephrotoxic medicines should be avoided.

Under (pre-) treatment with substances that may have adverse effects on the bone marrow (e.g. sulfonamides, trimethoprim-sulfamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Co-administration of medicines which cause folate deficiency (e.g. sulfonamides, trimethoprim-sulfamethoxazole) can lead to increased methotrexate toxicity. Particular caution should therefore also be exercised in the presence of existing folic acid deficiency.

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.

Oral hypoglycaemics, thiazide diuretics - possible reduced ABITREXATE excretion.

Particularly in the case of orthopaedic surgery where susceptibility to infection is high, a combination of methotrexate with immune-modulating medicines must be used with caution.

Concomitant administration of levetiracetam and methotrexate (e.g. ABITREXATE) has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two medicines.

The concurrent administration of medicines such as p-aminobenzoic acid and sulfinpyrazone will decrease the methotrexate transport function of renal tubules, thereby reducing excretion and almost certainly increasing ABITREXATE toxicity.

4.6 Fertility, pregnancy and lactation

ABITREXATE must not be used during pregnancy and in lactation. See section 4.3 and 4.8.

Contraception in males:

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of ABITREXATE.

4.7 Effects on ability to drive and use machines

ABITREXATE can cause dizziness, fatigue, blurred vision and eye-irritation, which may affect the ability to drive a vehicle or operate machinery.

4.8 Undesirable effects

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

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. This includes the use of calcium folinate (see sections 4.2 and 4.4). ABITREXATE therapy should only be resumed with particular caution, after careful consideration of the need for treatment and with increased vigilance for the possible recurrence of toxicity.

Most serious adverse reactions of ABITREXATE include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently observed adverse reactions of ABITREXATE include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite) and abnormal liver function tests (e.g. increased Alanine-aminotransferase (ALAT), Aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently occurring adverse reactions are leukopenia, anaemia, thrombocytopenia, headache, tiredness, drowsiness,

pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

The most relevant adverse reaction is suppression of the haematopoietic system and gastrointestinal disorders.

Other *frequently* occurring side effects are feeling unwell, inexplicable fatigue, chills and fever, dizziness and reduced resistance to diseases.

The undesirable effects with methotrexate are summarised by organ system.

Infections and infestations:

Frequent: Infections.

Less frequent: Opportunistic infections, respiratory or cutaneous bacterial infections, Herpes zoster, sepsis, neutropenic sepsis leading to fatality.

Frequency unknown: Sepsis resulting in death, *Pneumocystis carinii/jiroveci* pneumonia and other lung infection, reactivation of inactive chronic infections.

Neoplasms benign, malignant (including cysts and polyps):

Less frequent: Lymphoma[1], ABITREXATE may trigger tumour lysis syndrome in patients with rapidly growing tumour.

Gastrointestinal disorders[4]:

Frequent: Stomatitis, anorexia, nausea, vomiting, diarrhoea, melena.

Less frequent: Gingivitis, heamatemesis gastrointestinal ulceration, bleeding and enteritis, pancreatitis. The effect of ABITREXATE on the intestinal mucosa has led to malabsorption or toxic megacolon, dyspepsia, abdominal pain.

Frequency unknown: Mucositis.

Blood and the lymphatic system disorders:

Frequent: openia.

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.

Less frequent: Lymphoproliferative disorders (partly reversible), hypogammaglobulinaemia, bone marrow depression manifested by anaemia and thrombocytopenia.

Frequency unknown: Pancytopenia, eosinophilia, megaloblastic anaemia, hematopoietic disorders, lymphadenopathy, neutropenia, agranulocytosis, aplastic anaemia, immunosuppression, or any combination may occur. Infection or haemorrhage from various sites.

Hepato-biliary disorders:

Frequent: Elevated transaminase concentrations.

Less frequent: Chronic (fibrosis and cirrhosis) hepatotoxicity, resulting in acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis, liver cirrhosis or death usually following chronic administration, acute hepatitis. Hepatic toxicity resulting in increase alkaline phosphatase and bilirubin, decrease in serum albumin, hepatic failure, reactivation of chronic hepatitis or death.

Immune system disorders:

Less frequent: Anaphylactic type reaction.

Frequency unknown: Allergic reaction, anaphylactic shock.

Endocrine disorders:

Less frequent: Diabetes mellitus.

Psychiatric disorders:

Less frequent: Depression, confusion.

Frequency unknown: Mood alteration, transient subtle cognitive dysfunction, insomnia, psychoses.

Nervous system disorders:

Frequent: Headache, dizziness, fatigue.

Less frequent: Drowsiness, aphasia, hemiparesis, paresis and convulsions (following administration of higher doses), irritation, dysarthria, lethargy, ataxia, paraesthesia/hypoaesthesia.

Frequency unknown: Unusual cranial sensations.

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, usually transient, with paraplegia involving one or more spinal nerve roots
- oencephalopathy with confusion, agitation, somnolence, ataxia, dementia and sometimes serious conclusion.

Eye disorders:

Less frequent: Conjunctivitis, blurred vision.

Frequency unknown: Retinopathy.

Ear and labyrinth disorders:

Tinnitus.

Cardiac disorders:

Less frequent: Pericardial effusion, pericarditis.

Frequency unknown: Myocardial ischemia.

Vascular disorders:

Less frequent: Epistaxis, hypotension, thromboembolic events (arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, pulmonary embolus), vasculitis.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Pneumonitis acute or chronic, interstitial pneumonitis often associated with blood eosinophilia (can be fatal), chronic interstitial obstructive lung disease, interstitial fibrosis, dyspnoea, pharyngitis[2], pulmonary fibrosis, Pneumocystis carinii – pneumonia, pleuritis, dry cough.

Frequency unknown: Acute pulmonary oedema (after oral and intrathecal use), Syndrome consisting of pleuritic pain and pleural thickening has been reported following high doses, alveolitis, pulmonary alveolar haemorrhage[3], thoracic pain, pleural effusion, bronchial asthma, respiratory paralysis.

In the treatment of rheumatoid arthritis, Methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy. It is not always fully reversible.

Epistaxis has been reported.

Renal and urinary disorders:

Less frequent: Serious nephropathy or renal insufficiency, azotemia, dysuria, cystitis and haematuria.

Frequency unknown: Renal failure and uraemia may follow ABITREXATE administration, particularly after high doses or prolonged administration, ulceration of the urinary bladder, disturbed micturition, oliguria, anuria, proteinuria, electrolyte disturbance.

Pregnancy, puerperium and perinatal conditions:

Frequency unknown: Miscarriage, foetal damages and death.

Reproductive system and breast disorders:

Less frequent: Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction and vaginal discharge, infertility (reversible), suppression of spermatogenesis, loss of libido, impotence, vaginal ulceration, vaginal bleeding, gynaecomastia.

Frequency unknown: Vaginitis.

Skin and subcutaneous tissue disorders:

Frequent: Erythematous rash, alopecia.

Less frequent: Pruritis, urticaria, photosensitivity, depigmentation, ecchymosis, telangiectasia, acne, furunculosis, Steven Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, skin ulceration, painful damage to psoriatic lesion. Psoriatic lesions may worsen by exposure to UV-radiation. Radiation dermatitis and sunburn may flare up by ABITREXATE administration.

Frequency unknown: Skin exfoliation / dermatitis exfoliative +, onycholysis, petechia, allergic vasculitis, hidradenitis, herpetiform eruptions of the skin, hyperpigmentation of the nails and acute paronychia.

Musculoskeletal and connective tissue disorders:

Less frequent: Osteoporosis, stress fractures, arthralgia, myalgia, increased rheumatic nodules.

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

General disorders and administration site conditions:

Frequency unknown: Oedema, fever, chills, wound healing impairment, asthenia.

Injury and poisoning:

Frequency unknown: Increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy.

1. Can be reversible (see section 4.4)
2. Refer to section 4.4
3. (Has been reported for methotrexate used in rheumatologic and related indications)
4. Gastrointestinal severe adverse reactions require often dose reduction. Ulcerative stomatitis and diarrhoea require discontinuation of ABITREXATE therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

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 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/Publications/Index/8

4.9 Overdose

See section 4.4 and 4.8.

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate, as contained in ABITREXATE. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions.

Folinic acid neutralises the immediate toxic effect of ABITREXATE on the bone marrow and is given by mouth, intramuscularly, by intravenous bolus injection, or by infusion as calcium folinate. When overdosage is suspected, the dose of calcium folinate should be at least as high as that of ABITREXATE and should be administered within the first hour; further doses are given as required.

When average doses of ABITREXATE have an adverse effect, the equivalent of 12 mg of folinic acid may be given intramuscularly every 6 hours for 4 doses. The majority of a dose is excreted unchanged in the urine within 24 hours. Bound ABITREXATE may be retained in the body for many months.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytotoxic Agents

Pharmacotherapeutic group: Immunosuppressive agents.

ATC code: L04AX03

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

5.2 Pharmacokinetic properties

When given in low doses, methotrexate is well absorbed from the gastrointestinal tract. Higher doses are less well absorbed. 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

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Potato starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Tablets: Store at or below 25 °C in well-closed containers and protect from light.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

ABITREXATE tablets are available in blister strips containing 10 tablets.

ABITREXATE tablets are available in white high-density polyethylene (HDPE) bottles with white pilferproof closures.

Each bottle contains 30 or 100 tablets.

6.6 Special precautions for disposal and other handling

Women who are pregnant, planning to be or breastfeeding should not handle ABITREXATE.

Parents, care givers and patients should be advised to keep methotrexate out of the reach of children, preferably in a locked cupboard

Accidental ingestion can be lethal for children.

Anyone handling ABITREXATE should wash their hands after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling ABITREXATE.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

2090

8. REGISTRATION NUMBER(S)

ABITREXATE 2,5 mg TABLETS: 37/26/0466

ABITREXATE 10 mg: S/26/338

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2005

10. DATE OF REVISION OF THE TEXT

21 March 2021