PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MEXATE 2,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methotrexate disodium equivalent to 2,5 mg methotrexate.

Excipients with known effect:

Each tablet contains 6 mg lactose monohydrate and 49 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Yellow, round, uncoated tablets, with 'L2' debossed on one side and a score line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anti-neoplastic chemotherapy:

MEXATE is indicated for the treatment of breast carcinoma, gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. MEXATE is also indicated for the palliation of acute and subacute lymphocytic and meningeal leukaemia. Efficiency has been observed in palliation of acute lymphoblastic (stem cell) leukaemias.

In combination with corticosteroids MEXATE may be used for induction of remission.

MEXATE is also effective in the treatment of the advanced stages of lymphosarcoma, particularly in those cases in children and in advanced cases of mycosis fungoides.

High-dosage therapy (see section 4.4 below):

Diseases treated with high doses, administered in the form of single medicine or combination therapy, include osteogenic sarcoma, acute leukaemia, bronchogenic carcinoma and epidermoid carcinoma of the head and neck.

Psoriasis chemotherapy (see section 4.4 below):

Due to the high risk associated with its use, MEXATE is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or dermatological consultation.

Rheumatoid arthritis (RA):

MEXATE is indicated in the treatment of selected adult patients with severe, classical rheumatoid arthritis not adequately responsive to other forms of therapy, as confirmed by rheumatological consultation. Aspirin, nonsteroidal anti-inflammatory medicines, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs, including salicylates, has not been fully explored. Steroids may be reduced gradually in patients who respond to MEXATE. Combined use of MEXATE with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic medicines, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

4.2 Posology and method of administration

Posology

Anti-neoplastic chemotherapy:

Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

For conversion of mg/kg body mass to mg/m^2 of body surface or the reverse a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Choriocarcinoma and similar trophoblastic diseases:

MEXATE is administered orally in doses of 15 mg to 30 mg daily for a 5-day course. Such courses are usually repeated 3 to 5 times as required, with a rest period of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin hormone (CGH), which should return to normal or less than 50 IU/24 hours, usually after the 3rd or 4th course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of MEXATE after normalisation of CGH is usually recommended. Before each course of MEXATE careful clinical assessment is essential.

Cyclic combination therapy of MEXATE with other antitumour medicines has been reported as being useful.

Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with MEXATE has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. MEXATE is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Breast carcinoma:

Prolonged cyclic combination chemotherapy with cyclophosphamide, MEXATE and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes.

Leukaemia:

Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present-day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging.

MEXATE alone or in combination with steroids was formerly used for induction of remission of lymphoblastic leukaemias. More recently corticosteroid therapy in combination with other anti-leukaemic medicines or in cyclic combination therapy including MEXATE has produced rapid and effective remissions. When used for induction, MEXATE 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. MEXATE 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:
MEXATE is administered twice weekly by mouth in doses of 30 mg/m^2.

If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regime. Various experts have recently introduced a variety of dosage schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic medicines. Multiple medicine therapy with several medicines, including MEXATE, given concomitantly is gaining increasing support in both the acute and chronic forms of leukaemia. The medical practitioner should familiarise himself with the new advances in anti-leukaemic therapy.

Acute granulocytic leukaemia is rare in children but common in adults. This form of leukaemia responds poorly to chemotherapy and remissions are short with relapses common and resistance to therapy develops rapidly.

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 (CSF) which contains leukaemic cells in such cases.

Therefore, the CSF should be examined in all leukaemic patients.

The passage of MEXATE from blood serum to the cerebrospinal fluid is minimal; for adequate therapy the medicine is administered intrathecally. Some medical practitioners have given such chemotherapy in a prophylactic regime but the value of this procedure has not been established.

A common approach is to treat such patients as which may actually manifest leukaemic involvement by direct intrathecal instillation of MEXATE.

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

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character.

MEXATE given by intrathecal route appears significantly in the systemic circulation and may cause systemic MEXATE toxicity. Therefore, systemic antileukaemic therapy with the medicine should be appropriately adjusted, reduced or discontinued. Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas:

In Burkitt's tumour, stages I – II, MEXATE has produced prolonged remissions in some cases. Recommended dosage is 10 mg to 25 mg per day orally for 4 to 8 days. In stage III, MEXATE is commonly given concomitantly with other antitumour medicines. Treatment in all stages usually consists of several courses of the medicine interposed with 7 to 10 day rest periods.

Lymphosarcomas in stage III may respond to combined medicine therapy with MEXATE given in doses of 0,625 mg/kg to 2,5 mg/kg daily. Hodgkin's disease responds poorly to MEXATE and to most types of chemotherapy.

Mycosis fungoides:

Therapy with MEXATE appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2,5 mg to 10 mg daily orally 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 haematological monitoring. Methotrexate, as in MEXATE, has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

High-dosage therapy:

As stated under section 4.4, the recent published literature should be consulted for details. Dosage regimens have varied considerably in different studies; the nature and severity of the disease and the previous experience of the investigator are some of the factors influencing the choice of dosage and the duration of therapy.

It must be emphasised that high dosages should be used only by qualified specialists and in hospitals where the necessary facilities are available.

Leucovorin rescue schedules following treatment with higher doses of MEXATE:

Clinical situation	**Laboratory findings**	**Leucovorin dosage and duration**
Normal MEXATE elimination	Serum MEXATE level approximately 10 micromolar at 24 hours after administration, 1 micromolar	15 mg orally, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of MEXATE infusion).

	at 48 hours, and less than 0,2 micromolar at 72 hours.	
Delayed late MEXATE elimination	Serum MEXATE level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 15 mg orally, IM or IV every 6 hours, until MEXATE level is less than 0,05 micromolar.
Delayed early MEXATE elimination and/or evidence of acute renal injury	Serum MEXATE 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 MEXATE 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 MEXATE level is less than 1 micromolar; then 15 mg IV every 3 hours, until MEXATE level is less than 0,05 micromolar.

Alternatively, levofolinic acid, the pharmacologically active isomer of leucovorin (folinic acid), can be used for MEXATE rescue.

Guidelines for levofolinic acid MEXATE rescue dosage and administration:

Clinical situation	**Laboratory findings**	**Levofolinic acid dosage and duration**
Normal MEXATE elimination	Serum MEXATE level approximately 10 micromolar	7,5 mg orally, IM or IV every 6 hours for 60 hours (10

	at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	doses starting at 24 hours after start of MEXATE infusion).
Delayed late MEXATE elimination	Serum MEXATE level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 7,5 mg orally, IM or IV every 6 hours, until MEXATE level is less than 0,05 micromolar.
Delayed early MEXATE elimination and/or evidence of acute renal injury	Serum MEXATE level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR 100 % or greater increase in serum creatinine level at 24 hours after MEXATE 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 MEXATE level is less than 1 micromolar; then 7,5 mg IV every 3 hours until MEXATE level is less than 0,05 micromolar.

Psoriasis and rheumatoid arthritis chemotherapy:

THE PATIENT SHOULD BE FULLY INFORMED OF THE RISKS INVOLVED AND SHOULD BE UNDER CONSTANT SUPERVISION OF THE MEDICAL PRACTITIONER.

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver

function studies and liver biopsy, if indicated) before beginning MEXATE and periodically during MEXATE therapy, and before reinstituting MEXATE therapy after a rest period.
Appropriate steps should be taken by male and female patients to avoid conception during and for at least eight weeks following MEXATE therapy.

There are two commonly used general types of dosage schedules:

1) Weekly oral or parenteral intermittent large doses.
2) Divided dose intermittent oral schedule over a 36-hour period.

All schedules should be continually tailored to the individual patient. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5 – 10 mg parenterally.

For the treatment of psoriasis, the recommended starting dose schedules for a 70 kg adult:

1) Weekly single oral dose schedule: 10 – 25 mg per week until adequate response is achieved. With this dosage schedule, 30 mg per week should ordinarily not be exceeded.
2) Divided oral dose schedule: 2,5 mg at 12-hour intervals for three doses or at 8-hour intervals for four doses each week. With this dosage schedule, 30 mg per week should not be exceeded.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of medicine and to the longest possible rest period.
The use of MEXATE may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid arthritis:

Oral, 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

Oral, initially 10 mg once a week, the dosage being increased as necessary up to 20 mg per week.

Folate supplementation:

In patients with rheumatoid arthritis, including polyarticular-course juvenile rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce MEXATE toxicities such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes; see section 4.5 – Vitamin preparations.

Before taking a folate supplement, it is advisable to check vitamin B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of vitamin B_{12} deficiency.

Method of administration

MEXATE is administered orally.

4.3 Contraindications

- Hypersensitivity to methotrexate or to any of the excipients listed in section 6.1.
- Severe/significant renal impairment (creatinine clearance < 30 mL/min) for methotrexate doses < 100 mg/m^2, and moderate renal impairment (creatinine clearance < 60 mL/min) for methotrexate doses > 100 mg/m^2 (see section 4.2), or significant hepatic impairment.
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis; active infectious disease; and overt or laboratory evidence of immunodeficiency syndrome(s).
- Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive MEXATE.
- Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive MEXATE.

- Patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anaemia, should not receive MEXATE.
- Serious cases of anaemia, leucopenia or thrombocytopenia. MEXATE should not be used concomitantly with medicines with antifolate properties (e.g. co-trimoxazole).
- Methotrexate, as in MEXATE, is teratogenic and should not be given during pregnancy or to mothers who are breastfeeding (see section 4.6).
- Following administration to a man or woman, conception should be avoided by using an effective contraceptive method for at least 3 months after using MEXATE (see sections 4.4 and 4.6).
- Active infectious disease.
- Severe acute or chronic infections and immunodeficiency syndrome.
- During MEXATE therapy concurrent vaccination with live vaccines must not be carried out.

4.4 Special warnings and precautions for use

MEXATE SHOULD BE USED ONLY BY MEDICAL PRACTITIONERS EXPERIENCED IN ANTIMETABOLITE CHEMOTHERAPY.

Use in psoriasis and in rheumatoid arthritis (RA)

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

While in general a low dose of MEXATE 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, MEXATE 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, MEXATE is taken once weekly (see section 4.2).
The medical practitioner 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 MEXATE 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 or intermediate reversal of any cirrhosis usually requires discontinuation of therapy.
Although mild changes usually are no reason to avoid or discontinue therapy, MEXATE 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 leucoencephalopathy after intravenous administration of MEXATE to patients who underwent craniospinal irradiation.
Neurotoxic reactions are especially associated with the intrathecal use of methotrexate.
Chronic leucoencephalopathy was also reported in patients with osteosarcoma who were administered high dosages of MEXATE with calcium folinate rescue therapy, even without cranial irradiation. Discontinuation of MEXATE treatment does not always result in complete recovery.
A transient acute neurological syndrome has been observed in patients who underwent high-dose MEXATE 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 MEXATE 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 MEXATE the following laboratory tests are generally advised: haemograms, 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: haematology monthly, 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 MEXATE should be used with care, or not at all. If any clinically significant drop in blood cell count occurs, MEXATE 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 MEXATE 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).
MEXATE should be used with extreme caution in debility, extreme youth (see section 4.2), elderly patients (see section 4.2) 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

MEXATE 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 MEXATE 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, MEXATE 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 MEXATE.

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

The combined administration of MEXATE 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 MEXATE.

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 MEXATE, liver biopsies should be performed.

Haematological effects (myelosuppression)

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

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

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

Respiratory effects

Lung function tests may be useful in case a MEXATE-induced lung disease is suspected, in particular when initial base line values are available. MEXATE-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, hypoxaemia and infiltration in lung radiography may require treatment interruption and thorough examination. An infection should be excluded. In the treatment of MEXATE-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 MEXATE used in rheumatological 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

MEXATE 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, MEXATE 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 MEXATE 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 MEXATE 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 leucopenia occurring during treatment, bacterial infections could set in. When infection occurs, discontinuation of MEXATE 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 MEXATE has some immunosuppressive activity.
Vaccination with live vaccines is contraindicated during MEXATE 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 MEXATE elimination time is increased in renal dysfunction.
High dosages of MEXATE may cause renal toxicity and acute renal insufficiency. Nephrotoxicity is usually caused by the deposition of MEXATE 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 MEXATE and urinary excretion should be monitored.

Precipitation of MEXATE 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 patients), 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 MEXATE. If there is a severe fall in the white cell or platelet counts, MEXATE should be withdrawn.

Effects on fertility and reproduction (see section 4.6)

During MEXATE therapy and until at least three months after treatment with MEXATE 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 MEXATE by rheumatoid arthritis patients are limited.

Fertility

Methotrexate, contained in MEXATE, 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 MEXATE, causes embryotoxicity, abortion and fetal 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-oncological indications, the absence of pregnancy must be confirmed before MEXATE 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 MEXATE. Spontaneous remission may occur when MEXATE therapy is stopped; therefore, treatment with oncolytics is not necessarily indicated. First, it is necessary to stop MEXATE treatment when this adverse event occurs. If remission fails to appear, an adequate treatment has to be started.

MEXATE 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/leucoencephalopathy have occurred in cancer patients treated with methotrexate (e.g. MEXATE), 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 leucovorin (folinic acid) rescue.

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

The interactions of MEXATE 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 B_{12} prior to initiating folic acid supplementation, particularly in adults aged over 50 years, as folic acid intake may mask a vitamin B_{12} 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 doses of MEXATE (see section 4.8).

When concurrent administration of MEXATE 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.

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. leflunomide) is not advisable. Due to the possibility of fatal or severe toxic reactions, the patient should be fully informed by the medical practitioner of the risks involved and be under constant supervision.

Psoriatic lesions may get worse if MEXATE is combined with ultraviolet radiation/photochemotherapy (PUVA).

Lactose: MEXATE tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MEXATE tablets.

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 MEXATE (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 MEXATE by trimethoprim/sulfamethoxazole has been reported, probably by additional folic acid antagonism. The combined use of MEXATE and sulphonamides is therefore strongly advised against.

The use of nitrous oxide potentiates the effect of methotrexate, as in MEXATE, 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.

Azapropazone – excretion of methotrexate reduced.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or simultaneously with high-dose MEXATE treatment (> 10 mg methotrexate per week).
Increased serum levels of MEXATE have been reported at simultaneous administration of some NSAIDs with high-dose MEXATE resulting in death by serious haematological or gastrointestinal toxicity.
NSAIDs, salicylates and other weak organic acids, like probenecid, can lower tubular secretion of MEXATE resulting in increased toxicity. Use of MEXATE with these medicines should be made carefully under strict supervision. The potential toxicity of MEXATE is increased in particular with simultaneous use of NSAIDs when diuretics are also used. In rheumatology, a combination therapy of low-dose MEXATE and NSAID is commonly used.

Methotrexate dosage should be monitored if concomitant treatment with aspirin, ibuprofen or indometacin (NSAIDs) is commenced, as concomitant use of NSAIDs has been associated with fatal methotrexate toxicity.

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

Caution required

Care should be taken in combining high-dose MEXATE 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 MEXATE (re-) absorption.
Ciprofloxacin – excretion of methotrexate possibly reduced (increased risk of toxicity).
Penicillin – reduced excretion of methotrexate – increased risk of toxicity (haematological and gastrointestinal).
Doxycycline, sulphonamides, tetracyclines – increased risk of methotrexate toxicity.

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 MEXATE.

Digoxin absorption decreased by cytotoxics, as contained in MEXATE.

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.

Corticosteroids – increased risk of haematological toxicity.

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

Cytotoxics – increased risk of pulmonary toxicity (see sections 4.4 and 4.8).

Leflunomide (immunosuppressant) – risk of toxicity (see section 4.4).

Theophylline – methotrexate 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 haemotoxic effects of MEXATE.

Omeprazole and pantoprazole – excretion of MEXATE 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).

Triamterene – bone marrow suppression and reduced folate concentrations have been reported when triamterene and MEXATE 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. sulphonamides, trimethoprim-sulfamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Co-administration of medicines which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulfamethoxazole) can lead to increased methotrexate toxicity. 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 MEXATE. Preliminary human and animal studies have shown that after intravenous administration of calcium folinate a small amount penetrates the cerebrospinal fluid, predominantly as 5-methyltetrahydrofolate, and this amount is a factor 1 to 3 lower than the normal MEXATE concentration after intrathecal administration. Nevertheless, high doses of calcium folinate may lower the effectivity of intrathecally administered MEXATE. Folate deficiencies may increase MEXATE toxicity.

Oral hypoglycaemics, thiazide diuretics – possible reduced MEXATE 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. MEXATE) 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 MEXATE toxicity.

4.6 Fertility, pregnancy and lactation

MEXATE must not be used during pregnancy and in lactation (see sections 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 MEXATE.

Pregnancy:

Methotrexate is contraindicated during pregnancy (see section 4.3).

MEXATE can cause fetal death, embryotoxicity, abortion or teratogenic effects when administered to a pregnant woman. MEXATE is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis.

If pregnancy occurs during treatment with MEXATE 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 fetal development.

Breastfeeding:

MEXATE has been detected in human breast milk and is contraindicated during breastfeeding.

Fertility:

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

In oncological indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as MEXATE can be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

MEXATE may cause dizziness, fatigue, drowsiness, blurred vision and eye irritation (see section 4.8), which may affect the ability to drive a vehicle or operate machinery and to perform tasks requiring concentration.

4.8 Undesirable effects

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

The most frequently reported side effects include ulcerative stomatitis, leucopenia, nausea and abdominal distress. Other frequently reported side effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with MEXATE are listed below by organ system.

Infections and infestations:

Less frequent:	opportunistic infections, including fatal infections, sepsis
Frequency unknown:	infections, including pneumonia, *Pneumocystis carinii* pneumonia, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex

hepatitis, disseminated herpes simplex, fatal sepsis, cytomegalovirus infection, including cytomegaloviral pneumonia

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Less frequent: lymphoma, including reversible lymphoma

Blood and lymphatic system disorders:

Less frequent: anaemia, suppressed haematopoiesis, thrombocytopenia, aplastic anaemia

Frequency unknown: lymphadenopathy and lymphoproliferative disorders (including reversible), pancytopenia, neutropenia, agranulocytosis, eosinophilia

Immune system disorders:

Less frequent: anaphylactoid reactions, hypogammaglobulinaemia

Metabolism and nutrition disorders:

Less frequent: diabetes

Psychiatric disorders:

Less frequent: mood alterations, transient cognitive dysfunction

Nervous system disorders:

Less frequent: headache, hemiparesis, drowsiness, paresis, speech impairment (including dysarthria and aphasia), unusual cranial sensations

Eye disorders:

Less frequent: blurred vision, serious visual changes of unknown aetiology, conjunctivitis, transient blindness/vision loss

Cardiac disorders:

Less frequent: hypotension, pericardial effusion, pericarditis

Vascular disorders:

Less frequent: thromboembolic events (including thrombophlebitis, arterial thrombosis, cerebral thrombosis, deep vein thrombosis, pulmonary embolism, retinal vein thrombosis), vasculitis

Respiratory, thoracic and mediastinal disorders:

Less frequent: interstitial pneumonitis, including fatalities, pharyngitis, respiratory fibrosis, chronic obstructive pulmonary disease

Frequency unknown: alveolitis

Gastrointestinal disorders:

Less frequent: anorexia, diarrhoea, stomatitis, vomiting, pancreatitis, enteritis, gastrointestinal ulceration and bleeding, gingivitis, melaena, haematemesis

Hepato-biliary disorders:

Less frequent: liver enzyme elevations, acute hepatitis, chronic fibrosis and cirrhosis, hepatotoxicity, decrease in serum albumin

Frequency unknown: hepatic failure

Skin and subcutaneous tissue disorders:

Less frequent: alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), acne, ecchymosis, erythema multiforme, erythematous rashes, nodulosis, painful erosion of psoriatic plaques, photosensitivity, pigmentary changes, pruritus, skin ulceration, urticaria, furunculosis, telangiectasia

Musculoskeletal and connective tissue disorders:

Less frequent: arthralgia/myalgia, osteoporosis, stress fractures

Renal and urinary disorders:

Less frequent: severe nephropathy, renal failure, dysuria, azotaemia, cystitis, haematuria

Frequency unknown: proteinuria

Pregnancy, puerperium and perinatal conditions:

Less frequent: fetal defects, abortion

Frequency unknown: fetal death

Reproductive system and breast disorders:

Less frequent: menstrual dysfunction, defective oogenesis/spermatogenesis, impotence, infertility, loss of libido, transient oligospermia, vaginal discharge

General disorders and administration site conditions:

Less frequent: sudden death.

Adverse events in juvenile rheumatoid arthritis (JRA) studies:

The approximate incidences of adverse reactions reported in paediatric patients with JRA treated with oral, weekly doses of methotrexate as in MEXATE (5 to 20 mg/m^2/week or 0,1 to 1,1 mg/kg/week), were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory medicines, and some were also taking low doses of corticosteroids): elevated liver function tests, gastrointestinal reactions (e.g. nausea, vomiting, diarrhoea, stomatitis, leucopenia, headache, alopecia, dizziness and rash. Although there is experience with dosing up to 30 mg/m^2/week in JRA, the published data for doses above 20 mg/m^2/week are too limited to provide reliable estimates of adverse reaction rates.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of MEXATE is important. It allows continued monitoring of the benefit/risk balance of MEXATE. Health care providers are asked to

report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications:

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

4.9 Overdose

Leucovorin (folinic acid) is a specific antidote for methotrexate, as in MEXATE, and following accidental overdosage, should be administered within one hour at a dosage equal to, or greater than, the MEXATE dose. It may be administered by IV bolus or infusion. Further doses may be required. The patient should be observed carefully and blood transfusions, renal dialysis and reverse barrier nursing may be necessary.

In post-marketing experience, overdose with MEXATE has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose has also been reported.

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose in the self-administered dosage for rheumatoid arthritis and psoriasis (see sections 4.2 and 4.4). In these cases, events such as sepsis or septic shock, renal failure and aplastic anaemia were also reported.

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

Category and class: A 26 Cytotoxic agents.

Pharmacotherapeutic group: Immunosuppressive agents.

ATC code: L04AX03.

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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 % has been shown to be protein bound.

Elimination

Biphasic and triphasic plasma clearance has been shown. The majority of the dose is excreted within 24 hours in the urine, mainly unchanged, 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

Anhydrous lactose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep tablets in original container until required for use.

6.5 Nature and contents of container

White 60 mL HDPE round bottle closed with a 33 mm white PP child-resistant cap (CRC).

Pack size: 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion 0157

8. REGISTRATION NUMBER

54/26/0019

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

30 January 2024

10. DATE OF REVISION OF THE TEXT

Not revised yet.