

New Zealand Datasheet

1 PRODUCT NAME

TREXATE

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methotrexate 2.5 mg and 10 mg tablets

3 PHARMACEUTICAL FORM

TREXATE 2.5 mg tablets are yellow, circular, biconvex and uncoated. They are plain on both sides.

TREXATE 10 mg tablets are yellow, capsule shaped, biconvex and uncoated. They are plain on one side and are scored with a central break-line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic Chemotherapy

Treatment of breast cancer, gestational choriocarcinoma, and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic leukaemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukaemias. In combination with corticosteroids, TREXATE tablets may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. TREXATE tablets are also effective in the treatment of the advanced states (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

Psoriasis Chemotherapy

See section 4.4. Because of the high risk attending to its use, TREXATE tablets are 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 after dermatologic consultations.

4.2 Dose and method of administration

Antineoplastic Chemotherapy

Breast Cancer:

Good outcomes have been reported with prolonged adjuvant cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil following radical mastectomy in patients with primary breast cancer and positive axillary lymph nodes.

Choriocarcinoma and Similar Trophoblastic Diseases:

The recommended dose of TREXATE is 15–30 mg daily for five days. This course should be repeated three to five times, as required, until manifesting symptoms dissipate, with a rest of at least one week between courses.

Treatment is typically evaluated by 24-hour urinary chronic gonadotropin hormone (CGH) analysis, which should return to normal or <50 U/24h after the third or fourth course of TREXATE. It is usually recommended that TREXATE is continued for a further one or two courses following CGH normalisation. Measurable lesions should have completely resolved in six to eight weeks after initiating treatment.

The patient should undergo careful clinical assessment before initiating each treatment course.

Cyclic combination chemotherapy with methotrexate and other antitumour drugs has been reported to be useful. Prophylactic chemotherapy with methotrexate is recommended in patients with hydatidiform mole (including choriodenoma destruens, an invasive form of hydatidiform mole) as this may precede choriocarcinoma. The recommended dose and schedule of TREXATE in patients with similar trophoblastic diseases is the same as that in patients with choriocarcinoma.

Leukaemia:

Induction therapy with methotrexate 3.3 mg/m²/day in combination with prednisone 60 mg/m²/day produced remission in 50% of patients with lymphoblastic leukaemias, typically within a 4- to 6-week period.

After remission has been achieved and the patient's general clinical status has improved with supportive care, maintenance treatment with TREXATE 30 mg/m² twice weekly may be initiated. Methotrexate, alone or in combination with other agents, may be the drug of choice for maintaining drug-induced remissions. If relapse occurs, remission may be re-induced by repeating the initial induction regimen.

Lymphomas:

Methotrexate has produced long-lasting remission in some patients with stage I–II Burkitt's lymphoma. Stage III Burkitt's lymphoma is generally treated with methotrexate in combination with other antitumour agents. The recommended dosage of TREXATE for Burkitt's lymphoma is 10–25 mg/day for 4–8 days, followed by a 7- to 10-day rest period. Courses are typically repeated several times.

Stage III lymphosarcomas may respond to methotrexate in combination with other antitumour agents. The recommended dosage of TREXATE for stage III lymphosarcomas is 0.625–2.5 mg/kg/day.

Mycosis fungoides:

Approximately 50% of patients with mycosis fungoides achieve clinical remission with methotrexate. The recommended dosage of TREXATE for mycosis fungoides is 2.5–10 mg/day for weeks or months. Patient response and haematological monitoring should guide adjustment of the TREXATE dose and dosing regimen.

Psoriasis Chemotherapy

Patients with psoriasis treated with TREXATE should be under the supervision of a physician and should be fully informed of the risks involved with therapy.

TREXATE dosage and dosing regimen should be tailored to the individual patient on an ongoing basis. Patients should receive a test dose one week prior to commencing treatment to identify any idiosyncrasies.

TREXATE is typically initiated using one of the following dosing schedules (based on a typical adult weighing 70 kg):

1. *Weekly large doses:* TREXATE 10–25 mg/week until adequate response is achieved. Using this treatment regimen, TREXATE 50 mg/week should not be exceeded.
2. *Divided dose over 36 hours every week:* TREXATE 2.5–10 mg at 12 hour intervals for three doses or at 8 hour intervals for four doses each week. Using this treatment regimen, TREXATE 30 mg/week should not be exceeded.
3. *Daily oral dose with rest period:* TREXATE 2.5 mg/day for five days followed by a rest period of at least two days. Using this treatment regimen, TREXATE 6.25 mg/day should not be exceeded.

The dosage of TREXATE may be gradually adjusted to achieve optimal clinical response, but should not exceed the maximum dosage stated for each regimen. Once optimal clinical response has been achieved, the TREXATE dosage should be down-titrated to the lowest level possible with the longest rest period between doses possible. If TREXATE permits return to conventional topical therapy, this should be encouraged.

4.3 Contraindications

TREXATE is contraindicated in individuals with known hypersensitivity to methotrexate or any of the other ingredients in the tablets.

TREXATE is contraindicated in those patients with severe renal impairment.

In patients with psoriasis, the following conditions are contraindications for TREXATE: pregnancy, breast feeding, hepatic impairment, alcoholism, alcoholic liver disease, bone marrow depression or pre-existing blood dyscrasias (such as bone marrow hypoplasia, leukopenia, thrombocytopenia and anaemia), serious infections, overt or laboratory evidence of immunodeficiency, peptic ulcer disease and ulcerative colitis. If TREXATE is indicated as antineoplastic therapy, extreme caution should be exercised in patients with the aforementioned conditions.

TREXATE is contraindicated in combination with retinoids such as etretinate or acitretin, as the combination of methotrexate with these and has been shown to increase the risk of hepatitis.

4.4 Special warnings and precautions for use

In general, TREXATE should be initiated and administered under the supervision of a physician experienced in antimetabolite chemotherapy or in the case of non-oncological conditions, by a specialist doctor. Toxicity can occur at all dosages and with all treatment regimens. Deaths have been reported in patients treated with methotrexate for malignancy and psoriasis.

Before initiating TREXATE, the attending physician should fully inform patients of the potential benefits and risks of treatment including the possibility of fatal or severe toxic reactions the patient. Patients receiving TREXATE in the outpatient setting should be given information about the early signs and symptoms of toxicity and instructed to consult their physician promptly should such events occur.

Patients need to be closely monitored for toxicity, particularly those receiving TREXATE at high dosages or for long duration. In addition, particular attention should be given to patients with renal impairment, as methotrexate toxicity may cause renal failure. Methotrexate is eliminated slowly from third-space compartments and can result in a prolonged terminal phase half-life and unexpected toxicity. Patients with pleural effusions, ascites and other third-space compartments should be monitored carefully when using TREXATE, including regular measurements of plasma methotrexate levels. It may be necessary to evacuate third-space compartment fluid before treatment.

Patients should be informed about the need for close follow-up, including regular laboratory tests, when undergoing treatment with TREXATE. Complete blood cell count, haematocrit, urinalysis, hepatic function tests, renal function tests and chest x-ray should form part of routine assessment prior to initiating TREXATE. These assessments should also be conducted at appropriate points during therapy and after termination of therapy. More frequent monitoring may be required when the TREXATE dose is changed or during periods when there is increased risk of elevated methotrexate blood levels (e.g. dehydration).

In patients with psoriasis, haematological parameters should be monitored at least every month and renal and hepatic function should be monitored every one to two months during TREXATE treatment. Serum albumin, prothrombin time and other liver damage and function tests should be performed several times prior to TREXATE administration. Liver biopsy is required as patients with developing fibrosis or cirrhosis may be asymptomatic with normal liver function tests. Liver biopsy should be performed before the start of therapy or within 2–4 months of commencing treatment, after a total cumulative TREXATE dose of 1.5 g and after each additional 1.0–1.5 g. Fatty change, low-grade portal inflammation and other mild histological findings are relatively common before the start of therapy. TREXATE should be used with caution in such patients. Patients with mild fibrosis should undergo repeat biopsy after 6 months to assess further change. TREXATE should be discontinued in patients with moderate fibrosis or any cirrhosis.

In oncology patients, haematological, renal and hepatic parameters should be monitored more frequently than in psoriasis. Urine should be kept alkaline during TREXATE treatment. TREXATE should be used with caution, if at all, in patients with pre-existing bone marrow aplasia, leukopenia, thrombocytopenia or anaemia.

Malignant lymphomas that regress following TREXATE withdrawal may occur in patients receiving low-dose TREXATE. These do not require cytotoxic treatment. If a patient develops a malignant lymphoma, discontinue TREXATE first. Institute appropriate treatment if the lymphoma does not regress.

The risk of soft tissue necrosis and osteonecrosis is increased when TREXATE is given concomitantly with radiotherapy.

Patients treated with TREXATE, even at an apparent safe dosage, may experience marked depression of bone marrow, anaemia, aplastic anaemia, leukopenia, neutropenia, thrombocytopenia or bleeding. These events may have a sudden onset. Severe leukopenia increases the risk of bacterial infection. In the event of a profound drop in blood cell count, TREXATE should be immediately withdrawn and appropriate therapy initiated, such as antibiotics in the case of severe leukopenia and blood or platelet transfusion in the case of severe bone marrow depression.

The risk of reproductive effects with TREXATE should be discussed with all patients, irrespective of gender (see section 4.6).

In patients receiving TREXATE for psoriasis, the importance of the weekly dosing regimen should be reinforced by both the physician and the pharmacist, as mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity. The pharmacist should also exercise great care in ensuring that the correct strength of TREXATE tablet (2.5 mg or 10 mg) is administered to the patient.

Extreme caution and close monitoring should be exercised when using TREXATE in patients with debility or who are very young or old. Relatively low TREXATE dosages should be considered in elderly patients due to diminished hepatic and renal function together with decreased folate status.

Lactose is an excipient in TREXATE tablets. TREXATE should not be used in patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose–galactose malabsorption.

Special warnings and precautions apply to the following areas:

Infections

The immunosuppressive effects of methotrexate can potentially lead to serious or fatal infections, including *Pneumocystis carinii* pneumonia. Patients demonstrating signs or

symptoms of infection should be monitored carefully and aggressive antibiotic therapy may be required. Extreme caution should be exercised when using TREXATE in patients with active infections or where immune responses in a patient are important or essential. TREXATE is typically contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Vaccination may be ineffective when given during treatment with TREXATE and immunisation with live vaccines is generally not recommended. Disseminated vaccinia virus infections have been reported in patients administered smallpox immunisation while undergoing treatment with methotrexate.

Gastrointestinal Toxicity

Vomiting, diarrhoea and ulcerative stomatitis are frequent adverse effects with methotrexate and require interruption of therapy. These events may increase the risk of haemorrhagic enteritis and death from intestinal perforation; therefore, TREXATE should be discontinued in patients with severe or recurrent vomiting, severe or recurrent diarrhoea or extensive ulcerative stomatitis. Extreme caution should be exercised when using TREXATE in patients with peptic ulcer or ulcerative colitis.

Hepatotoxicity

Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Methotrexate is frequently associated with transient elevated transaminase levels, which do not usually require TREXATE dosing modification. Histological changes on liver biopsy have been shown after sustained methotrexate use, with liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis reported. Prolonged treatment (for two years or more) and high cumulative methotrexate doses (1.5 g or more) have been associated with chronic hepatotoxicity (fibrosis and cirrhosis), which is potentially fatal. In patients with psoriasis, the risk of developing acute hepatitis or chronic hepatotoxicity appears to be correlated with comorbidities such as alcoholism, obesity and diabetes, advanced age and exposure to arsenical compounds, as well as cumulative methotrexate dose.

Liver biopsy is the only reliable method of evaluating methotrexate-induced hepatotoxicity at present; however, as changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined, by liver function tests which should be performed before TREXATE initiation and monitored regularly throughout treatment. Special caution should be exercised when using TREXATE in patients with pre-existing liver damage or impaired liver function. Patients with significant decreases and/or persistent abnormalities in serum albumin levels should be further evaluated, as these may be markers of serious hepatotoxicity. Concomitant administration TREXATE with alcohol and other drugs with hepatotoxic potential should be avoided.

Pulmonary Toxicity

Acute or chronic interstitial pneumonitis and pulmonary fibrosis, which can progress rapidly and is potentially fatal and other methotrexate-induced lung disease may occur at any time during methotrexate treatment and at all doses of methotrexate. Such pulmonary lesions are potentially life-threatening or fatal and are not always completely reversible. Typical symptoms of methotrexate-induced lung disease include fever, cough, chest pain, dyspnoea and hypoxaemia. Lung infiltrates may be apparent on x-ray. Pneumonia (in some cases leading to respiratory failure) and potentially fatal opportunistic infections (such as *Pneumocystis carinii* pneumonia) may occur with methotrexate therapy.

Patients treated with TREXATE should be closely monitored for pulmonary symptoms. Patients treated with TREXATE who develop pulmonary symptoms (particularly a dry, non-productive cough and dyspnoea) should have TREXATE treatment discontinued. Pneumonia (including *Pneumocystis carinii* pneumonia) and other pulmonary infections need to be

considered.

Neurotoxicity

Significant central nervous system toxicity may occur in patients treated with systemic high doses of methotrexate. Patients should be closely monitored for neurological signs and symptoms. If a patient develops neurological signs and symptoms, TREXATE should be discontinued and appropriate therapy initiated.

Skin Toxicity

Photosensitivity reactions may occur with methotrexate; therefore, TREXATE recipients should avoid excessive unprotected exposure to the sun or sunlamps.

Renal Function

TREXATE is typically contraindicated in patients with severe impaired renal function. While methotrexate is not nephrotoxic, it is almost completely excreted by the kidney. Unchanged methotrexate and its metabolite (7-hydroxy methotrexate) can precipitate in the kidney, causing renal damage that leads to acute renal failure. Patients should receive adequate oral hydration and urine alkalinisation (methotrexate tends to precipitate at pH less than 6) and should have serum methotrexate and creatinine levels periodically measured to reduce the risk of renal damage. Renal function tests should be performed periodically. TREXATE dose should be reduced or the drug discontinued in patients with impaired renal function until function is improved or restored.

4.5 Interaction with other medicines and other forms of interaction

Other cytotoxic drugs are often used in combination with methotrexate. If drugs with similar pharmacological effects are used, additive toxicity may occur. Bone marrow depression and renal, gastrointestinal and pulmonary toxicity should be carefully monitored. If TREXATE is used in combination with drugs with overlapping toxicities, the dosage of TREXATE should be adjusted.

If TREXATE is used in combination with oral antibiotics (such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics), methotrexate absorption from the gastrointestinal tract may be reduced or antibiotics may inhibit bowel flora, suppressing bacterial metabolism of methotrexate and interfering with the enterohepatic circulation.

Methotrexate is partly bound to serum albumin following absorption. If TREXATE is used in combination with drugs competing for the same albumin binding site or inhibiting albumin binding (such as salicylates, sulfonamides, sulfonyleureas, phenytoin, phenylbutazone, aminobenzoic acid and some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid and chloramphenicol), methotrexate may be displaced, increasing plasma concentrations and the risk of toxicity. Methotrexate may also preferentially bind to hypolipidaemic compounds (such as cholestyramine) than serum proteins.

Probenecid diminishes renal tubular transport; therefore, patients receiving concomitant TREXATE and probenecid should be carefully monitored. The renal clearance of methotrexate may be reduced by penicillins and sulfonamides, leading to increased serum methotrexate concentrations causing haematological and gastrointestinal toxicity. Patients receiving concomitant TREXATE and penicillins or sulfonamides should be carefully monitored.

Caution should be exercised with concomitant administration of lower dosages of TREXATE and non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates. In an animal model, these drugs reduced tubular secretion of methotrexate. Concomitant administration of methotrexate (typically high dose) with some NSAIDs (including aspirin and other salicylates, azapropazone, diclofenac, indomethacin and ketoprofen) has resulted in reports of unexpectedly severe,

sometimes fatal, bone marrow suppression, aplastic anaemia and gastrointestinal toxicity. While the mechanism of this toxicity has yet to be completely elucidated, it may involve displacement of methotrexate from protein-binding sites or a significant decrease in renal blood flow as a consequence of NSAID inhibition of prostaglandin E2 synthesis, leading to reduced methotrexate excretion. While there is no evidence to support an effect of naproxen on the pharmacokinetics of methotrexate, a fatal interaction has been reported in a patient receiving these drugs concomitantly.

Pyrimethamine and trimethoprim/sulfamethoxazole may decrease tubular secretion and have an additional anti-folate effect, leading to increased bone marrow suppression when used concurrently with methotrexate. There have been reports of bone marrow suppression and decreased folate levels when methotrexate is administered concomitantly with triamterene.

TREXATE should not be administered concomitantly with multivitamin preparations including folic acid or its derivatives, as these may alter responses to methotrexate.

L-asparaginase may antagonise the activity of methotrexate.

Concurrent administration of methotrexate with etretinate, azathioprine, retinoids, leflunomide, sulfasalazine, alcohol and other potential hepatotoxins may increase the risk of hepatotoxicity. Concurrent administration of methotrexate and leflunomide may also increase the risk of pancytopenia and interstitial pneumonitis.

The effects of methotrexate on folate metabolism may be potentiated by nitrous oxide anaesthesia, leading to severe and unpredictable myelosuppression and stomatitis. Folinic acid rescue may reduce this effect.

Ulcerated skin lesions may occur in psoriasis patients receiving methotrexate and concomitant amiodarone.

There have been several reports of skin cancer in patients with psoriasis or mycosis fungoides receiving methotrexate concomitantly with PUVA therapy (methoxalen and ultraviolet light).

The plasma levels of mercaptopurine may increase when administered concomitantly with methotrexate. The dosage of TREXATE may need adjustment if used in combination with mercaptopurine.

Patients receiving 24-hour methotrexate infusion have experienced enhanced toxicity when administered packed red blood cell transfusions, probably as a consequence of prolonged high serum methotrexate concentrations. Care should be exercised when administering packed red blood cells concurrently with TREXATE.

Methotrexate is an immunosuppressant and may reduce the immunological response to concurrent vaccination. If a live vaccine is administered concurrently with methotrexate, a severe antigenic reaction may occur.

When theophylline is administered concurrently with TREXATE, theophylline levels should be monitored, as methotrexate may reduce the clearance of this drug.

Drug Interactions with Proton Pump Inhibitors (PPI)

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as ameprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to

methotrexate toxicities.

4.6 Fertility, pregnancy and lactation

Pregnancy

TREXATE is contraindicated in the treatment of psoriasis in women who are pregnant.

Use of methotrexate in pregnant women has caused embryotoxicity, abortion, foetal death and/or congenital abnormalities. Fertility impairment, oligospermia and menstrual dysfunction have also been reported during methotrexate treatment and for a short period after therapy has been withdrawn. It should not be used in pregnant women, or those who might become pregnant, unless the potential benefits can be expected to outweigh the considered risks.

Abnormal or immobile spermatozoa have been reported in men receiving methotrexate in clinical studies.

Pregnancy should be excluded in women of childbearing potential before commencing TREXATE. Men and women treated with TREXATE should be advised to use appropriate contraception during TREXATE treatment and for a minimum of 3 months after cessation of therapy, although the optimal time interval between discontinuation of methotrexate in either partner and conception has not been clearly established. Patients who become pregnant while receiving TREXATE or who receive TREXATE during pregnancy should be given information on the potential serious hazard to the foetus with methotrexate exposure.

Breast feeding

TREXATE is contraindicated in breast-feeding women as methotrexate is excreted in breast milk and could potentially cause serious adverse events in the infant.

Fertility

Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during methotrexate therapy. In cancer chemotherapy, methotrexate should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.

Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving methotrexate.

4.7 Effects on ability to drive and use machines

Patients receiving TREXATE should be advised that methotrexate can cause dizziness or fatigue that may affect ability to drive or use machines.

4.8 Undesirable effects

Toxicities associated with methotrexate are often unavoidable and occur as a consequence of methotrexate acting on normal, rapidly-proliferating tissues, particularly the bone marrow and gastrointestinal tract. Adverse effects with methotrexate are generally reversible if detected early.

The earliest indications of toxicity with methotrexate are typically ulcerations of the oral mucosa. Common adverse events include stomatitis, leukopenia, thrombocytopenia, nausea and abdominal distress. Other events include malaise, undue fatigue, chills and fever, headaches, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection. The frequency and intensity of different toxicities is influenced by different dosages and routes of administration of methotrexate.

Haematological Toxicity

Methotrexate is associated with bone marrow depression, leukopenia, neutropenia, thrombocytopenia, anaemia (including aplastic anaemia), eosinophilia, pancytopenia, agranulocytosis, hypogammaglobulinaemia, lymphadenopathy, proliferative disorders and decrease in serum albumin. Two nadirs in leukocyte and neutrophil count may occur: the first after 4–7 days and the second after 12–21 days, followed by recovery. Haematological toxicity may contribute to fever, infection, haemorrhage and septicaemia.

Megaloblastic anaemia has been reported with methotrexate, predominantly in elderly patients receiving weekly treatment for a long period of time. Folate supplementation may resolve anaemia, allowing methotrexate treatment to continue.

Gastrointestinal Toxicity

Gastrointestinal effects associated with methotrexate include mucositis (stomatitis, gingivitis, glossitis, pharyngitis and enteritis), nausea, vomiting and diarrhoea. These events may lead to ulceration and bleeding of oral or gastrointestinal mucosal membranes, intestinal perforation, haematemesis, malaena, abdominal distress and anorexia. Rare cases of malabsorption or toxic megacolon have been reported with methotrexate.

Hepatotoxicity

Acute and chronic hepatotoxicities associated with methotrexate include acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or hepatic cirrhosis and pancreatitis. Increases in transaminase and lactate dehydrogenase levels are commonly reported with methotrexate, but typically resolve within one month after cessation of therapy. Patients exposed to high cumulative doses or long-term therapy (2 years or more) may develop hepatic fibrosis or cirrhosis. The cumulative dose of the drug as well as the presence of comorbidities such as alcoholism, obesity, diabetes, advanced age and exposure to arsenical compounds increases the risk of chronic hepatotoxicity in patients with psoriasis.

Hypersensitivity and Dermatological Toxicity

Methotrexate has been associated with anaphylactic reactions, erythematous rashes, urticaria and pruritus. Other dermatological events that have occurred in patients treated with methotrexate include dermatitis, acne/furunculosis/folliculitis, nail changes, vasculitis, petechiae, ecchymoses, telangiectasia, photosensitivity, skin depigmentation or hyperpigmentation and alopecia. For 1 or 2 days following each methotrexate dose, burning and erythema may present in psoriatic areas, aggravated by concurrent ultraviolet radiation exposure. Recall radiation dermatitis or sunburn may also occur following methotrexate exposure.

Some severe and occasionally fatal dermatological adverse events have occurred within days of single or multiple doses of methotrexate in patients with neoplastic and non-neoplastic diseases. These events include toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin ulceration/necrosis and erythema multiforme.

Pulmonary Toxicity

Methotrexate has been associated with interstitial pneumonitis, interstitial fibrosis and reversible eosinophilic pulmonary infiltrates. Occasional cases of chronic interstitial pulmonary disease have been reported. Methotrexate-induced pulmonary toxicity may manifest as fever, cough that is typically dry and non-productive, dyspnoea, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (typically diffuse and/or alveolar).

Cardiovascular Toxicity

Methotrexate has been associated with pericarditis, vasculitis, pericardial effusion, hypotension and thromboembolic events, including arterial thrombosis, cerebral thrombosis,

deep vein thrombosis, retinal vein thrombosis thrombophlebitis and pulmonary embolism.

Central Nervous System Toxicity

Methotrexate has been associated with headaches, drowsiness, blurred vision, eye discomfort, tinnitus, convulsions, speech impairment including dysarthria, lethargy, motor dysfunction, cranial nerve palsies, aphasia, hemiparesis, cranial nerve palsies, leucoencephalopathy, encephalopathy, arachnoiditis, coma, dementia, depression and confusion. Occasional cases of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensation has been reported with low doses of methotrexate.

Urogenital and Reproductive Toxicity

Methotrexate has been associated with severe nephropathy, renal failure, azotemia, cystitis, dysuria and haematuria. There have also been reports of defective oogenesis or spermatogenesis, transient oligospermia, urogenital dysfunction, menstrual dysfunction, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence, infertility, abortion, foetal defects and foetal death in patients receiving methotrexate.

Carcinogenicity

The risk of developing secondary tumours may increase with exposure to cytotoxic drugs. Chromosomal damage has been observed in animal somatic cells and human bone marrow cells exposed to methotrexate (see section 5.3).

Other Adverse Effects

Methotrexate has also been associated with metabolic changes, precipitating diabetes and osteoporotic effects, including aseptic necrosis of the femoral head. Cases of abnormal tissue cell changes, arthralgia/myalgia, proteinuria, nodulosis, stress fracture and even sudden death have also been reported with methotrexate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Haematological and gastrointestinal reactions and other symptoms and signs that occur at pharmacological methotrexate dosages are commonly reported following oral methotrexate overdose. In particular, leukopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, gastrointestinal ulceration, gastrointestinal bleeding, anorexia, progressive weight loss and bloody diarrhoea are seen. Death has been reported following methotrexate overdose, as a consequence of events such as sepsis or septic shock, renal failure and aplastic anaemia.

If overdosage occurs, consider administration of activated charcoal. This is most effective when given within one hour of methotrexate ingestion. If the patient is not fully conscious or has an impaired gag reflex, it may be necessary to protect the airway then administer activated charcoal through a nasogastric tube.

As soon as possible after an inadvertent overdose of methotrexate occurs, initiate intravenous or intramuscular calcium folinate (leucovorin calcium) 10 mg/m² every 6 hours until serum methotrexate levels are less than 10⁻⁸M. If the patient has gastric stasis or obstruction, administer calcium folinate parenterally. The patient should receive concomitant hydration (3 l/day) and urinary alkalinisation with sodium bicarbonate to achieve a urinary pH of 7 or more. Serum creatinine and methotrexate levels should be monitored at 24-hour intervals. If the 24-

hour serum creatinine level is 50% higher than baseline, 24-hour methotrexate level is $>5 \times 10^{-6}\text{M}$ or 48-hour methotrexate level is $\geq 9 \times 10^{-7}\text{M}$, increase the calcium folinate dose to 100 mg/m^2 every 3 hours until serum methotrexate levels are less than 10^{-8}M . The calcium folinate infusion rate should be 16.0 ml/min ($160 \text{ mg calcium folinate/min}$) or less. Patients with significant third space accumulations are high risk and should be monitored until serum methotrexate levels are less than 10^{-8}M , irrespective of 24-hour serum methotrexate concentration.

If high-dose methotrexate has been administered, the above statements on calcium folinate dosage do not apply. Dosages have varied in different studies and published literature on high-dose methotrexate should be consulted.

If massive methotrexate overdosage occurs, hydration and urinary alkalinisation may be required to prevent the precipitation of methotrexate and its metabolites in the renal tubules. Acute, intermittent haemodialysis using a high-flux dialyzer has been shown to facilitate effective clearance of methotrexate. Methotrexate elimination is not significantly improved with standard haemodialysis or peritoneal dialysis, although some clearance of methotrexate may occur if the patient is completely anuric and there are no other therapeutic options available. The Poisons Information Centre should be contacted on 0800 764766 for management of a TREXATE overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressive agents, ATC code: L04AX03

Mechanism of Action

Methotrexate (4-amino-10 methyl folic acid) is an analogue of folic acid and an anti-metabolite. Methotrexate is actively transported into the cell and binds almost irreversibly to dihydrofolate reductase, an enzyme that catalyses the reduction of folic acid to tetrahydrofolic acid. Decreased levels of tetrahydrofolic acid interferes with DNA synthesis, DNA repair and cell replication. The affinity of methotrexate for dihydrofolate reductase is far greater than the affinity of folic acid or dihydrofolic acid for dihydrofolate reductase; therefore, the effects of methotrexate are not reversible by folic acid, even when given in large doses. Methotrexate also increases intracellular deoxyadenosine triphosphate, which inhibits ribonucleotide reduction and polynucleotide ligase activity, an enzyme involved in DNA synthesis and repair. Malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, spermatogonia, urinary bladder cells and other actively proliferating tissues are typically more sensitive to the pharmacological effects of methotrexate.

5.2 Pharmacokinetic properties

Absorption

Peak serum methotrexate levels are reached within 1–4 hours of oral methotrexate administration. Methotrexate administered at low oral dosages (up to $25\text{--}30 \text{ mg/m}^2$) is rapidly absorbed from the gastrointestinal tract. However, when methotrexate is administered at higher dosages, absorption is erratic, possibly owing to a saturation effect. Absorption of oral methotrexate may also be affected by drug-induced epithelial denudation, motility changes and alterations in intestinal flora. Food may also delay methotrexate absorption and reduce peak concentration.

Distribution

Serum protein reversibly binds to approximately 50% of absorbed methotrexate. Absorbed

methotrexate is actively transported across cell membranes into tissue cells, with highest concentrations found in the kidneys, gallbladder, spleen, liver and skin. Following oral or parenteral administration, small or insignificant levels of methotrexate cross the blood–brain barrier and enter the cerebrospinal fluid. Greater methotrexate concentrations are found in the cerebrospinal fluid when methotrexate is administered at higher dosages. Small amounts of methotrexate have also been detected in saliva and blood milk. Methotrexate crosses the placenta. Methotrexate slowly enters into pleural effusions, ascites, marked tissue oedemas and other third space compartments.

Even a single therapeutic dose of methotrexate results in the drug being retained for several weeks in the kidney and several months in the liver. Repeated daily doses may lead to sustained serum concentrations and tissue accumulation.

Metabolism

Methotrexate does not appear to undergo significant metabolism when administered at low doses. At high doses, methotrexate is converted to polyglutamated forms by hepatic and intracellular metabolism and can then be converted back to methotrexate by hydrolase enzymes. At commonly-prescribed dosages, a small amount of methotrexate may be converted to the 7-hydroxy derivative.

Before methotrexate is absorbed, it may be metabolised by gastrointestinal flora to a pharmacologically inactive metabolite, 2,4-diamino-N10-methylpteroic acid.

Excretion

Methotrexate appears to undergo triphasic clearance from the plasma. During the first phase, methotrexate is likely to be distributed to the organs; during the second phase, methotrexate undergoes renal excretion; and during the third phase, methotrexate passes into the enterohepatic circulation.

After low oral doses, the terminal half-life of methotrexate is between 3 and 10 hours. There is wide intra-individual variation in methotrexate clearance, with average total clearance of 12 l/h. Delayed clearance of methotrexate is one of the major contributors to drug toxicity.

Methotrexate is primarily excreted through the kidneys by glomerular filtration and active transport, although dosage influences the pattern of elimination. Patients with impaired renal function often have prolonged methotrexate excretion and greater methotrexate accumulation. Concurrent administration of salicylates and other weak organic acids may also suppress methotrexate clearance. Methotrexate is eliminated slowly from third-space compartments and can result in a prolonged terminal phase half-life and increased risk of toxicity.

5.3 Preclinical safety data

In mice and rats, the intraperitoneal median lethal dose (LD50) of methotrexate was 94 and 6–25 mg/kg, respectively. In rats, the oral LD50 was 180 mg/kg. In mice, tolerance to methotrexate increased with age. In dogs, an intravenous dose of methotrexate 50 mg/kg was lethal. After a single dose of methotrexate, the main targets were the hemolymphopoietic system and the gastrointestinal tract.

In mice and rats administered multiple doses of methotrexate, the main targets were the hemolymphopoietic system, gastrointestinal tract, lung, liver, kidney, testes and skin. Tolerance to chronic methotrexate increases with age.

Carcinogenicity

The risk of developing secondary tumours in humans increases with exposure to cytotoxic drugs. The risk of neoplasia with methotrexate has not been evaluated in controlled studies;

however, as with other cytotoxic drugs, methotrexate must be considered potentially carcinogenic.

The carcinogenic potential of methotrexate has been evaluated in a number of preclinical studies, with inconclusive results. Methotrexate has been shown to induce chromosomal damage in animal somatic cells and human bone marrow cells. In several preclinical tests, methotrexate was genotoxic. It was also shown to be toxic to male reproductive organs, embryotoxic and teratogenic in mice, rats and rabbits. In life-span studies in mice and hamsters, there was no evidence of carcinogenicity with methotrexate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Dibasic calcium phosphate, Sodium starch glycollate, Microcrystalline cellulose, Purified talc, Magnesium stearate.

6.2 Incompatibilities

Methotrexate is incompatible with cytarabine, fluorouracil and prednisolone.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage

TREXATE should be stored below 25°C and protected from light.

6.5 Nature and contents of container

TREXATE 2.5 mg tablets are available in PVC/Al blister packs of 30 tablets or 90 tablets.

TREXATE 10 mg tablets are available in PVC/Al blister packs of 50 tablets or 90 tablets.

6.6 Special precautions for disposal

Pregnant individuals should not work with TREXATE.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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Mt Wellington
AUCKLAND.
Ph (09) 574 6060
Fax (09) 574 6070

9 DATE OF FIRST APPROVAL

21 March 2013

10 DATE OF REVISION OF THE TEXT

20 December 2017

TREXATE is a registered trademark of Rex Medical Ltd.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Fertility section added
4.8	Reporting of adverse events added
4.9	Poison information centre contact added