New Zealand Datasheet

WARNINGS
Methotrexate may cause significant toxicities which may be fatal including haematological, hepatic, renal, pulmonary, gastrointestinal, dermatological, and immune-related. See section 4.4.
In psoriasis and rheumatoid arthritis, the importance of **once weekly dosing** should be emphasized. Mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity.

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 adults 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.

Rheumatoid Arthritis chemotherapy
Methotrexate is indicated in the management of severe, recalcitrant, active rheumatoid arthritis in adults that is not adequately responsive to other forms of therapy.

4.2 Dose and method of administration

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

If applicable, the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

Antineoplastic Chemotherapy

Methotrexate should only be used in oncology indications by clinicians with the appropriate expertise.

The application and dosage recommendations for the administration of methotrexate for different oncology indications varies. The following regimens below are only examples.

The latest published protocols and local guidelines should be consulted before initiating treatment.

Depending on the regimen, the dose of methotrexate may be calculated per m2 body surface area (BSA). The dose must be adjusted carefully depending on the body surface area.

Fatal cases of intoxication have been reported after administration of incorrectly calculated doses. Special attention must be given to dose calculation.

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 mg to 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 less than 50 units/24 hours 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 chorioadenoma destruens, an invasive form of hydatidiform mole) as this may precede choricarcinoma. 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/m^2/day in combination with prednisone 60 mg/m^2/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/m^2 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 to 25 mg/day for 4 to 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 to 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 to 10 mg/day for weeks or months. Patient response and haematological monitoring should guide adjustment of the Trexate dose and dosing regimen.

Psoriasis and rheumatoid arthritis Chemotherapy

Important warning about the dosage of methotrexate

In patients receiving methotrexate for psoriasis or rheumatoid arthritis, 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.

Weekly dosing prescriptions should specify a particular day of the week. Prescribers should advise the patient of the dosing regimen for their awareness and obtain at least verbal indication from the patient that they have understood the dosing regimen.

Pharmacists should clearly indicate the dosing regimen on the dispensing label at the point of dispensing and obtain at least a verbal indication from the patient that they have understood the dosing regimen. 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.

General
Patients with psoriasis or rheumatoid arthritis treated with Trexate should be under the supervision of a specialist physician, and should be fully informed of the risks involved with therapy.

Methotrexate should be started at a low dose and gradually increased to achieve the optimal clinical response, taking into consideration potential toxicities.

Once the optimal clinical response has been achieved, the dosage should be gradually reduced to the lowest possible effective maintenance dose.

Patients should be monitored regularly for treatment response and toxicity and treatment tailored accordingly.

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.

Psoriasis chemotherapy
Recommended dose schedules for a 70 kg adult:

The effective weekly dose is generally between 10 and 25 mg/week. Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed a maximum dose of 25mg/week.

Doses exceeding 20 mg/week can be associated with significant increase in toxicity. Use of such doses should be carefully considered by the physician taking into account the risks and benefits.

The dosage of Trexate may be gradually adjusted to achieve optimal clinical response, but should not exceed the maximum dosage. Once optimal clinical response has been achieved, the Trexate dosage should be down-titrated to the lowest effective maintenance dose.

Rheumatoid arthritis chemotherapy
The recommended initial dosage of methotrexate is 7.5 mg once weekly. Therapeutic response can be expected within three to six weeks and the patient may continue to improve for another twelve weeks or more. The dosage may be increased to 15 mg/week after six weeks in non-responsive patients.

If necessary, dosage may be gradually increased further to achieve optimal response, up to a maximum of 20 mg/week. Once the optimal clinical response has been achieved, the dosage should be gradually reduced to the lowest possible effective maintenance dose.

The optimal duration of therapy is unknown. Limited data available from long term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

Special note – changing between formulations
Use of methotrexate via the parenteral route for psoriasis or rheumatoid generally is considered in individuals with an inadequate response to oral therapy, who do not tolerate oral administration, who exhibit inadequate absorption of the oral form of methotrexate, or when higher doses are required.

When changing from oral to parenteral administration, a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Special populations

Patients with renal impairment
Methotrexate is excreted to a significant extent by the kidneys, and therefore should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). Dose adjustment may be needed to prevent the accumulation of the medicine.

When used for non-oncological indications, the following dose adjustments are recommended.

Creatinine clearance	Dose
>60	100%
30 - 59	50%
< 30	Contraindicated

Further adjustment may be needed depending on the individual patient. A lower initial dose and a more gradual dose increase is also recommended in renal impairment. Renal function should be closely monitored.

When used for oncology indications, use of methotrexate in renal impairment and dose adjustment in renal impairment may be variable. Consult local guidelines/protocols.

Use in hepatic impairment
Methotrexate should be administered only with the greatest caution, if at all, in patients with

pre-existing liver disease, especially if due to alcohol. Dose adjustment may be needed. See also section 4.4.

Methotrexate is contraindicated in patients with significantly impaired hepatic function.

Patients who have low albumin levels, such as those with poor nutritional status, may be at greater risk of toxicity.

When used for oncology indications, consult local guidelines/protocols.

Use in children
Aside from use in cancer chemotherapy, the safety and efficacy of methotrexate in children has not been fully elucidated. Trexate is not recommended in paediatric patients.

In oncology use, treatment should follow currently published therapy protocols for children.

Use in elderly
Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, lower doses should be considered, and these patients should be closely monitored (see Section 4.4).

4.3 Contraindications

Methotrexate is contraindicated in the following:

- Known hypersensitivity to methotrexate or any of the active excipients.
- Pregnancy and breastfeeding (see section 4.6)
- Significantly impaired renal function
- Significantly impaired hepatic function
- Alcoholism
- Bone marrow depression or pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenic, or anaemia
- Severe acute or chronic infections
- Overt or laboratory evidence of immunodeficiency syndrome
- Stomatitis, ulcers of the oral cavity, known active gastrointestinal ulcer disease
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.
- Combination use of methotrexate and retinoids due to increased risk of hepatitis.

4.4 Special warnings and precautions for use

Precautions before starting treatment

General

In general, methotrexate 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 methotrexate, 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 methotrexate 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 should also be informed of the need for close follow-up and ongoing monitoring, including regular laboratory tests to monitor for toxicity.

Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because the toxic effects can occur at any time during therapy, it is necessary to follow the patients on methotrexate therapy very closely.

Before beginning treatment or resuming treatment after a recovery period

Perform a full blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, renal function tests, and chest X-ray. Evaluate for personal and family history of liver disease, personal history of alcohol use or gastrointestinal ulcerative conditions.

If clinically indicated, tuberculosis and hepatitis B and C should be excluded.

In women of childbearing age, rule out pregnancy.

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 methotrexate, including regular measurements of plasma methotrexate levels. It may be necessary to evacuate third-space compartment fluid before treatment.

During treatment

Monitoring

Monitor full blood count, liver function and renal function tests, and signs and symptoms of possible toxicity. The frequency of monitoring of these parameters depends on the indication for use, dose regimen and individual patient. Local guidelines should be followed.

For patients receiving low dose methotrexate in non-oncologic conditions, full blood count,,renal and liver functions tests should generally be taken weekly until therapy is stabilised, thereafter every 1- 3 months throughout treatment.

More frequent monitoring may be necessary during the initial phase of treatment, when the dose is increased and during episodes of a higher risk of elevated methotrexate blood levels (e.g., dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as NSAIDs). Closer monitoring is also necessary especially in patients taking other hepatotoxic or haematotoxic or renal toxic medicinal products (see section 4.5), and also in elderly patients.

Patients should also be monitored often for signs and symptoms of methotrexate toxicity as outlined below.

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the dose should be reduced or the medicine discontinued, and appropriate corrective measures taken. If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of the benefits and risks of treatment, and with increased alertness as to possible recurrence of toxicity.

In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes. Folic acid or folinic acid supplementation may be considered according to current treatment guidelines.

If acute methotrexate toxicity occurs, which may occur at any dose, patients may require folinic acid. It is important to determine any increase in methotrexate levels within 48 hours of therapy, for treatment with folinic acid, otherwise irreversible methotrexate toxicity may occur. See also section 4.9.

Folinic acid deficiency

Folate deficiency states may increase methotrexate toxicity. Before taking a folate supplement,

it is advisable to check B12 levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B12 deficiency.

Hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs)

Concomitant use of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs, e.g., leflunomide) is not advisable.

Pregnancy and breastfeeding

Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age prior to initiating methotrexate (see section 4.6).

Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short time after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration. The risk of reproductive effects with methotrexate should be discussed with all patients, irrespective of gender (see section 4.6).

Methotrexate is contraindicated in pregnancy and breastfeeding (see section 4.3 and section 4.6).

For males, reliable contraception is recommended during and for at least three months after the end of the treatment. For females, reliable contraception is recommended during and for at least six months after end of the treatment (see section 4.6).

Organ system toxicity

Haematologic

Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia, thrombocytopenia and bleeding. Clinical sequelae such as fever, sore throat, flu-like symptoms, infections, abnormal bruising and haemorrhage from various sites and septicaemia may be expected. Patients should be encouraged to report signs and symptoms of these if occur.

Methotrexate should not be used in patients with pre-existing haematopoietic impairment (see section 4.3).

Pre-treatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of the common effect of haematopoietic suppression. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate discontinuation and appropriate therapy.

If profound leucopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression. In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood cell counts.

Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances (see section 4.5, Antibiotics, Oral antibiotics).

Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term weekly methotrexate therapy.

Infections
The immunosuppressive effects of methotrexate can potentially lead to serious or fatal infections, including Pneumocystis carinii pneumonia.

Patients should be advised to report all symptoms or signs suggestive of infection. Patients demonstrating signs or symptoms of infection should be monitored carefully and aggressive antibiotic therapy may be required and methotrexate treatment is generally interrupted.

Methotrexate should be used with extreme caution in the presence of active infections, and use is contraindicated in severe acute or chronic infections. Methotrexate is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes (see section 4.3). .

Potentially fatal opportunistic infections especially Pneumocystis jirovecii pneumonia may occur with methotrexate therapy. This factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

Pneumonia (in some cases leading to respiratory failure) may occur. When a patient presents with pulmonary symptoms, the possibility of Pneumocystis jirovecii pneumonia should be considered.

Special attention should be paid in cases of inactive chronic infections (e.g herpes zoster, TB, hepatitis B or C) because of their potential for re-activation. These may occur after treatment has been discontinued.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Immunisation
Vaccination may be ineffective when given during treatment with methotrexate. Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections and are therefore contraindicated.

Gastrointestinal Toxicity
Vomiting, diarrhoea and ulcerative stomatitis are frequent adverse effects with methotrexate and require interruption of therapy and supportive therapy (including preventing dehydration) should be instituted until recovery occurs. These events may increase the risk of haemorrhagic enteritis and death from intestinal perforation; therefore, methotrexate should be discontinued in patients with severe or recurrent vomiting, severe or recurrent diarrhoea or extensive ulcerative stomatitis Use of methotrexate is contraindicated in patients with peptic ulcer or ulcerative colitis (see section 4.3).

If haematemesis, black discoloration of the stool or blood in stool occur, therapy is to be interrupted. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Conditions leading to dehydration such as emesis, diarrhoea or stomatitis, can increase the toxicity of methotrexate due to elevated levels of the active substance.

Examine the oral cavity and throat for mucosal change. Encourage patients to report any potential signs for gastrointestinal toxicity such as signs of stomatitis or diarrhoea and vomiting. Gastrointestinal disorders frequently require dosage adjustment.

Hepatotoxicity
Methotrexate is contraindicated in severe hepatic impairment, particularly if alcohol related (see section 4.3). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Methotrexate may cause acute and chronic hepatotoxicity, particularly at high dosage or with

prolonged therapy, including liver atrophy, necrosis, hepatic cirrhosis, acute hepatitis, fatty changes and periportal fibrosis. Transient and asymptomatic elevations of liver enzymes are frequently seen after methotrexate administration and are usually not a reason for modification of methotrexate therapy or predictive of subsequent hepatic disease.

Persistent abnormalities in liver function tests, and/or significant decreases in serum albumin, and/or symptoms/signs of liver toxicity may be indicators of serious liver toxicity and require evaluation.

Chronic (fibrosis and cirrhosis) liver toxicity is potentially fatal and may occur following prolonged (2 years or longer) treatment and high cumulative drug doses of at least 1.5 grams in non-oncological indications.

Particular attention should be given to the appearance of liver toxicity, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. Liver function should be determined prior to initiation of treatment and monitored regularly throughout therapy.

Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Clinical and laboratory evaluation should be performed to evaluate pre-existing liver disease in patients with prior hepatitis B or C infections. Based on these evaluations, treatment with methotrexate may not be appropriate for some patients.

The primary risk factors for severe liver damage, due to methotrexate hepatotoxicity, include: previous liver disease, repeatedly abnormal liver function tests, alcohol consumption/abuse, hepatopathy (including chronic hepatitis B or C), and a family history of hepatopathy. Secondarily risk factors (with possibly lower relevance) for methotrexate hepatotoxicity include diabetes mellitus (in patients treated with insulin), obesity and exposure to hepatotoxic medicines or chemicals. Additional hepatotoxic medicinal products should not be taken during the treatment of methotrexate unless clearly necessary and with close monitoring. The consumption of alcohol should be avoided (see section 4.5).

In studies in psoriatic patients, hepatotoxicity appeared to be correlated not only to the cumulative dose of the drug but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds.

Treatment should not be instituted or should be discontinued if any abnormalities of liver function tests are present or develop during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. Temporary increases in transaminases to 2 – 3 x ULN have been reported by patients. In the case of a constant increase in liver-related enzyme, a reduction of the dose or discontinuation of therapy should be considered.

Methotrexate should be discontinued if no other reasons for the elevations are found, and the elevations remain above the normal limits.

The need for liver biopsy should be evaluated on an individual basis and national recommendations should be followed.

Pulmonary Toxicity

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. It may occur at any time throughout treatment, and at any dose. Particular caution is required in patients with impaired pulmonary function.

Acute or chronic interstitial pneumonitis and pleural effusion, often associated with blood eosinophilia, may occur and deaths have been reported.

Rheumatoid arthritis patients are at risk of developing rheumatoid lung disease, which is often associated with interstitial pulmonary disease. Methotrexate may exacerbate this

underlying lung disease.

Pulmonary symptoms (especially a dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, thoracic pain, chest pain, dyspnoea, hypoxaemia and an infiltrate on x-ray. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded in patients presenting with symptoms of pulmonary toxicity.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Patients should be closely monitored for pulmonary signs and symptoms at each follow-up visit and be informed of the risk of pneumonitis. Patients should be advised to contact their doctor immediately should they develop persistent cough, dyspnoea, fever or if they experience symptoms of spitting or coughing up blood.

Pulmonary function tests may be useful if lung disease (e.g., interstitial pneumonitis) is suspected, especially if baseline measurements are available.

Methotrexate should be discontinued from patients with pulmonary symptoms and a thorough investigation undertaken to exclude infection and tumors, including a chest x-ray. The possibility of pneumocystis jiroveci pneumonia should be taken into account.

If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted. Methotrexate-induced pulmonary toxicity may not be fully reversible.

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, methotrexate should be discontinued and appropriate therapy initiated.

Skin Toxicity

Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's syndrome), and erythema multiforme have been reported with methotrexate.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

Photosensitivity reactions and increased risk of skin cancer (non-melanoma and melanoma) may occur with methotrexate; therefore, methotrexate recipients should avoid excessive unprotected exposure to the sun or sunlamps.

Patients receiving immunosuppressive therapy, including methotrexate, are at an increased risk of developing skin cancer (melanoma and non-melanoma). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer and exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Renal Function

Methotrexate is contraindicated in patients with severe impaired renal function. Caution and use of lower doses are recommended in renal impairment (see section 4.2).

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. Renal function should be closely monitored before, during and after treatment. Impaired renal function may result in methotrexate accumulation in toxic amount or even additional renal damage. Methotrexate dose should be reduced or the drug discontinued in patients with impaired renal function until function is improved or restored.

Caution should be taken in situations where renal function may decline, such as concomitant use with nephrotoxic medicines or medicines that may affect the elimination of methotrexate (see also section 4.5) or dehydration. More frequent monitoring of renal function should be considered during times where acute change to renal function may occur, such as dehydration, vomiting, diarrhoea, or when new medicines that may be nephrotoxic are started, and in elderly patients.

Musculoskeletal
Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis

Other
Methotrexate, like other cytotoxic drugs, may trigger tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive and pharmacological measures may prevent or alleviate this complication.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. These lymphomas may regress following withdrawal of methotrexate without requiring treatment. Failure of the lymphoma to show signs of spontaneous regression requires initiation of cytotoxic therapy.

Information for patients
Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Patients should be informed of the risks in the use of methotrexate (including the early signs and symptoms of toxicity), of the need to see their physician promptly if they occur, and of the need for close follow-up, including regular laboratory tests to monitor toxicity.

Patients should be informed that the dose of methotrexate is once weekly in the treatment of psoriasis and rheumatoid arthritis (see Section 4.2). Patients should be aware of importance of adhering to the once weekly intake and that daily administration can lead to serious toxic effects.

Patients should be advised to report all symptoms or signs suggestive of infection.

Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea. Patients should be advised to contact their doctor immediately if they experience symptoms of spitting or coughing up blood.

Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions and increased risk of skin cancer (non-melanoma and melanoma).

Paediatric use
Cases of overdose by miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see section 4.2).

Use in elderly
Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasised to the patient that the recommended

dose is taken weekly for psoriasis or rheumatoid arthritis (see section 4.2).

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.

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

4.5 Interaction with other medicines and other forms of interaction

Other cytotoxic medicines
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 methotrexate is used in combination with drugs with overlapping toxicities, the dosage of methotrexate should be adjusted.

Antibiotics
If methotrexate 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.

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.

Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored. Probenecid diminishes renal tubular transport; therefore, patients receiving concomitant methotrexate 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 methotrexate and penicillins or sulfonamides should be carefully monitored.

Drugs highly bound to plasma proteins
Methotrexate is partly bound to serum albumin following absorption. If methotrexate is used in combination with drugs competing for the same albumin binding site or inhibiting albumin binding (such as salicylates, sulfonamides, sulfonylureas, 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.

NSAIDS (nonsteroidal anti-inflammatory drugs)
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.

Oncology use
Nonsteroid anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with high doses of methotrexate such as used in the treatment of osteosarcoma. NSAIDs elevate and prolong serum methotrexate levels, resulting in deaths from severe haematologic (including bone marrow suppression and aplastic anaemia) and gastrointestinal toxicity.

Non-oncology use
Caution should be exercised with concomitant administration of lower dosages of methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates.

Vitamins
In non-oncology conditions, concomitant treatment with folinic acid or folic acid may decrease the incidence or severity of adverse effects from methotrexate therapy. It is not known whether these medications may decrease the efficacy of methotrexate in treating arthritis. Because vitamin preparations containing folic acid or folinic acid may decrease the effectiveness or alter the responses to methotrexate these should not be given to patients taking methotrexate for other conditions.

L – asparaginase
L-asparaginase may antagonise the activity of methotrexate.

DMARDS (disease-modifying antirheumatic drugs)
Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, has not been studied and may increase the incidence of adverse effects.

Leflunomide
Concurrent administration of methotrexate and leflunomide may also increase the risk of pancytopenia and interstitial pneumonitis.

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

Hepatotoxic agents
An increased risk of hepatotoxicity has been reported when methotrexate and etretinate (a retinoid) are given concurrently (see section 4.3).

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., leflunomide, azathioprine, sulfasalazine and alcohol) should be closely monitored for possible increased risk of hepatotoxicity.

Haematotoxic agents
Administration of additional haematotoxic medicinal products increases the likelihood of severe haematotoxic adverse reactions to methotrexate.

Medicinal products that cause folic acid deficiency
Concomitant therapy with medicinal products that can cause folic acid deficiency can result in increased methotrexate toxicity. Particular caution should be exercised in patients with pre-

existing folic acid deficiency.

Nitrous oxide
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.

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

Diuretics
Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.

Phenytoin
Cytotoxic agents may impair absorption of phenytoin, which may decrease efficacy of phenytoin and increase the risk for exacerbation of convulsions. Risk of toxicity enhancement or lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin is possible.

Ciclosporin
Ciclosporin may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

PUVA therapy
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).

Red blood cells
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 methotrexate.

Vaccination
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.

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

Allopurinol
Concomitant use of allopurinol with methotrexate may result in an increased incidence of cytotoxic-induced bone marrow depression.

Sodium Valproate
Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

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 omeprazole, 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.

Assay for folate
Methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use of methotrexate is contraindicated throughout pregnancy.

Methotrexate has been shown to be teratogenic. Methotrexate has caused embryotoxicity, abortion, fetal death, intrauterine growth restriction and/or congenital abnormalities when administered to pregnant women.

Methotrexate is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits are expected to outweigh the considered risks.

Women of childbearing potential should not be started on methotrexate until any existing pregnancy is excluded with certainty, e.g., by pregnancy test prior to initiating therapy.

Both male and female patients should be fully counselled on the serious risk to the fetus if pregnancy occurs while undergoing treatment and counselled regarding pregnancy prevention and planning.

Pregnancy should be avoided and reliable effective contraception used if either partner is receiving methotrexate, during and for a minimum of six months after therapy has ceased for women and three months after therapy has ceased for men. The optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the medicine is used during pregnancy or if the patient becomes pregnant while taking methotrexate or up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and appropriate examinations should be performed.

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

Fertility
Methotrexate has been reported to cause impairment of fertility, defective oogenesis or spermatogenesis, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy.

Men treated with methotrexate should use contraception and not father a child during and for three months after treatment. Methotrexate may be genotoxic and has caused increased number of abnormal and immobile spermatozoa in clinical studies.

Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before

starting the therapy. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Where appropriate, women who are planning to become pregnant should be advised of possible options regarding fertility and genetic counselling.

The possible risks of effects on reproduction should be discussed with patients of childbearing potential.

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.

Table 1: Tabulated summary of adverse drug reactions

System organ class (SOC)	**Adverse reaction**
Infections and infestations	Infections (including fatal sepsis), decreased resistance to infection, opportunistic infections (sometimes fatal in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases). pneumonia, pneumocystis jirovecii pneumonia (most common infection), respiratory tract infection, cutaneous bacterial infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex hepatitis, disseminated herpes simplex cytomegalovirus infection (including cytomegaloviral pneumonia), reactivation of hepatitis B infection, worsening of hepatitis C infection.
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Lymphoma (including reversible lymphoma), tumour lysis syndrome, melanoma and non-melanoma skin cancer
Blood and lymphatic system disorders:	Bone marrow failure, Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, anaemia, aplastic anaemia, megaloblastic anaemia, eosinophilia, pancytopenia, agranulocytosis, lymphadenopathy, lymphoproliferative disorders (including reversible), haemorrhage (from various sites), septicaemia.
Immune system disorders:	Anaphylactoid reaction, anaphylactic reaction, hypogammaglobulinaemia
Metabolism and nutrition	Diabetes mellitus, metabolic disorder

disorders:	
Psychiatric disorders:	Depression, confusion, irritability, transient subtle cognitive dysfunction, mood alteration
Nervous system disorders:	Paraesthesia, headaches, dizziness, drowsiness, convulsions, aphasia, hemiparesis, speech impairment, paresis, dysarthria, lethargy, motor dysfunction, cranial nerve palsies, brain oedema, leucoencephalopathy, encephalopathy, CSF pressure increased, neurotoxicity, arachnoiditis, coma, paraplegia, stupor, ataxia, dementia, unusual cranial sensations, Guillain Barre Syndrome, hypoethesia, meningism, paralysis
Eye disorders:	Conjunctivitis, blurred vision, eye discomfort, serious visual changes of unknown aetiology including transient blindness/vision loss.
Ear and labyrinth disorders:	Tinnitus.
Cardiac disorders:	Pericarditis, pericardial effusion, pericardial tamponade, pulmonary oedema.
Vascular disorders:	Vasculitis, hypotension, thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis thrombophlebitis and pulmonary embolism).
Respiratory, thoracic and mediastinal disorders:	Pneumonitis, interstitial pneumonitis (including fatalities), respiratory fibrosis, interstitial pulmonary fibrosis, reversible eosinophilic pulmonary infiltrates, chronic interstitial obstructive pulmonary disease, pulmonary alveolar haemorrhage (has been reported for methotrexate used in rheumatologic and related indications), pharyngitis, alveolitis, pleural effusion, pleurisy, dyspnoea, chest pain, hypoxia, cough (especially dry and non-productive), respiratory failure.
Gastrointestinal disorders:	Mucositis, gingivitis, stomatitis, glossitis, decreased appetite, anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melaena, gastrointestinal ulceration (including oral ulcers) and bleeding, pancreatitis, intestinal perforation, noninfectious peritonitis, toxic megacolon, malabsorption, enteritis, change in sense of taste (metallic taste),
Hepatobiliary disorders	Hepatic failure, acute and chronic hepatotoxicity, acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, chronic fibrosis, hepatic cirrhosis, elevated liver enzymes, increase of transaminases and blood lactate dehydrogenase, decreased serum albumin. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month after cessation of therapy.
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, painful damage to psoriatic lesions, skin ulceration, skin necrosis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentation disorder (depigmentation/hyperpigmentation), alopecia, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes, nail hyperpigmentation, acute paronychia.
Musculoskeletal, connective tissue	Osteoporosis, osteonecrosis (aseptic necrosis of the femoral head), soft tissue necrosis, abnormal tissue cell changes, arthralgia/myalgia,

and bone disorders:	stress fracture, back pain, nuchal rigidity
Renal and urinary disorders:	Renal failure, severe nephropathy, dysuria, azotaemia, cystitis, haematuria, proteinuria, urogenital dysfunction.
Pregnancy, puerperium and perinatal conditions:	Abortion, fetal defects, fetal death
Reproductive system disorders:	Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, vaginal bleeding, vaginal ulceration, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence.
General disorders and administration site conditions:	Sudden death, increased rheumatoid nodules, pyrexia, chills, malaise, fatigue, oedema, peripheral oedema, wound healing impairment

Description of selected adverse reactions

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 to 7 days and the second after 12 to 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.

Heptatotoxicity
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). Reports of melanoma and non-melanoma skin cancer have been documented in patients treated with methotrexate.

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://pophealth.my.site.com/carmreportnz/s/.

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. Refer to the calcium folinate prescribing information for further information for dosing and administration.

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 methotrexate 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 tetrohydrofolic 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 to 4 hours of oral methotrexate administration. Methotrexate administered at low oral dosages (up to 25 to 30 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 to 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.

Not all pack sizes may be available.

6.6 Special precautions for disposal

Guidelines and procedures for appropriate handling and disposal of hazardous chemicals should be observed in the handling of cytotoxics.

Pregnant individuals should not work with Trexate.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Rex Medical Ltd
PO Box 18119
Glen Innes
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9 DATE OF FIRST APPROVAL

21 March 2013

10 DATE OF REVISION OF THE TEXT

27 September 2024
Trexate® is a registered trademark of Rex Medical Ltd.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
General	Addition of box warning at top of data sheet Data sheet update as requested by Medsafe.
4.1	Addition of Rheumatoid Arthritis indication
4.2	Addition of Rheumatoid Arthritis dosing information Additional information regarding regimens for oncology use Dosing in psoriasis chemotherapy: Deletion of dosing schedules that are not weekly dosing, reduced maximum weekly dose, Addition of note regarding changing between formulations Addition of special population information
4.3	Reformatted into a list
4.4	Additional safety information and complete update of this section.
4.5	Additional information and complete update of this section.
4.6	Update of pregnancy and fertility information
4.8	Addition of table of tabulated summary of adverse drug reactions
4.9	Deletion of dosing and administration information for calcium folinate and referral to the calcium folinate prescribing information.
6.5	Addition of not all pack sizes may be available.
6.6	Addition of cytotoxic warning.
6.7	Deleted