NEW ZEALAND DATA SHEET

WARNINGS

Methotrexate may cause significant toxicities which may be fatal including haematological, hepatic, renal, pulmonary, gastrointestinal, dermatological, and immune-related. See section 4.4 Special warnings and precautions for use.

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

Chexate 2.5 mg, 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg tablet contains 2.5 mg of methotrexate (as sodium).

Each 10 mg tablet contains 10 mg of methotrexate (as sodium).

Excipient of known effect:

Each 2.5 mg tablets and 10 mg tablets contain 82 mg and 328 mg of lactose monohydrate, respectively.

For the full list of excipients, see Section 6.1 List of excipients .

3 PHARMACEUTICAL FORM

2.5 mg tablet: Yellow, round, uncoated, flat tablet, with a cosmetic score line and engraved with ORN 57 on one side, diameter 6 mm.

The score line on the 2.5 mg tablet is only cosmetic and must not be used to divide the tablet into equal doses.

10 mg tablet: Yellow, capsule-shaped, convex, uncoated tablet, engraved with ORN 59 on one side and score on other side, length of 14 mm and width of 6 mm.

The 10 mg tablet can be divided into equal doses.

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, methotrexate may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. Chexate is also effective in the treatment of the advanced stages (III

and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

Psoriasis chemotherapy

(See Section 4.4 Special warnings and precautions for use)

Because of the high risk attending to its use, Chexate is 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

Dosage

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

Use in psoriasis and rheumatoid arthritis

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. Weekly dosage prescriptions should specify a particular day of the week.

Important warning about the dosage of Chexate In the treatment of psoriasis and rheumatoid arthritis, Chexate must only be used once a week. Dosage errors in the use of Chexate can result in serious adverse reactions, including death. Please read this section of the Product Information very carefully.

Prescribers should advise the patient of the dosing regimen for their awareness and obtain at least a 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.

Antineoplastic chemotherapy

Methotrexate should 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 m^2 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 carcinoma

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

Choriocarcinoma and similar trophoblastic diseases

The recommended dose is 15-30 mg daily for a five-day course. Such courses are usually repeated three to five times as required with a rest period of one or more weeks interposed between courses, until any manifesting toxic symptoms subside.

The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotrophin hormone (HCG), which should return to normal or less than 50 units/24 hour usually after the 3rd or 4th course and usually followed by a complete resolution of measurable lesions in 4 to 6 weeks.

One to two courses of methotrexate after normalisation of

HCG is usually recommended. Before each course of the drug, careful clinical assessment is essential.

Cyclic combination therapy of methotrexate with other antitumour drugs has been reported as being useful. Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukaemia

Methotrexate alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. When used for induction, in doses of 3.3 mg/m^2 in combination with prednisone 60 mg/m^2 given daily, remission occurred in 50% of patients treated, usually within a period of 4 to 6 weeks.

Methotrexate alone, or in combination with other agents, appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: methotrexate is administered in doses of 30 mg/m^2 twice weekly.

If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

Lymphomas

Burkitt's tumour, stages I-II: 10 to 25 mg per day orally for 4 to 8 days. Methotrexate has produced prolonged remission in some cases.

Burkitt's tumour stage III: methotrexate is commonly given concomitantly with other antitumour agents.

Lymphosarcomas stage III: Combined drug therapy with 0.625 mg to 2.5 mg/kg daily doses of methotrexate.

Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods.

Mycosis fungoides

Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months.

Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and haematologic monitoring.

Psoriasis and rheumatoid arthritis

General

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.

The dosage and dosing regimen should be tailored to the individual patient on an ongoing basis. An initial test dose one week prior to commencing treatment is recommended to identify any idiosyncrasies.

Psoriasis chemotherapy

The patient should be fully informed of the risks involved and should be under constant supervision of the physician.

All schedules should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy.

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

Rheumatoid arthritis

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.

Method of administration

Oral administration.

Special note – changing between formulations

Use of methotrexate via the parenteral route for psoriasis or rheumatoid arthritis 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

Renal impairment

Methotrexate is excreted primarily by the kidneys. In patients with renal impairment the dose may need to be adjusted to prevent accumulation of drug (see Section 4.4 Special warnings and precautions for use: Organ system toxicity, Use in renal impairment).

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.

Hepatic impairment

Methotrexate should not be used in patients with severe hepatic impairment or in patients who have a significant liver disease, particularly if this is/was alcohol-related (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

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.

Elderly

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.

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 (see Section 4.4 Special warnings and precautions for use: Use with caution in the following circumstances).

Paediatric population

Aside from use in cancer chemotherapy, the safety and efficacy of methotrexate in children has not been fully elucidated. In oncology use, treatment should follow currently published therapy protocols for children.

Cases of overdose by miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see Section 4.4 Special warnings and precautions for use: Use with caution in the following circumstances).

Patients with diabetes mellitus or lactose intolerance

Chexate tablets contain 82 mg of lactose monohydrate per 2.5 mg of methotrexate (See Sections 2 Qualitative and quantitative composition and 4.4 Special warnings and precautions for use). Physicians should consider whether the potential benefits of oral treatment outweigh the risks of sugar and lactose intake in patients with diabetes mellitus or lactose intolerance. Especially when high doses of methotrexate are required, parenteral formulations of other methotrexate products may be considered as an alternative to Chexate tablets.

Methotrexate dose	Lactose monohydrate from Chexate
2.5 mg	82 mg
7.5 mg	246 mg
10 mg	328 mg
15 mg	492 mg
25 mg	820 mg

Methotrexate dose	Lactose monohydrate from Chexate
30 mg	984 mg
45 mg	1476 mg
70 mg	2296 mg
100 mg	3280 mg
175 mg	5740 mg

4.3 CONTRAINDICATIONS

Chexate should not be given to:

- pregnant women (see Section 4.6: Use in pregnancy)
- breast-feeding women (see Section 4.6: Use in lactation)
- patients with severe hepatic impairment
- patients with severe renal impairment
- patients with alcoholism
- patients who have overt or laboratory evidence of immunodeficiency syndromes
- patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or anaemia
- patients with severe, acute or chronic infections
- patients with a known hypersensitivity to methotrexate or to any of the excipients
- patients with stomatitis, ulcers of the oral cavity, known gastrointestinal ulcer disease.

- During methotrexate therapy concurrent vaccinations with live vaccines must not be carried out.
- An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate with retinoids such as acitretin is also contraindicated.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Importance of weekly dosing in psoriasis and rheumatoid arthritis

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see **WARNINGS** box, Section 4.2 Dose and method of administration and 4.9 Overdose). Great care should be taken to ensure the correct Chexate tablet strength is dispensed to the patient. Chexate is available as 2.5 mg and 10 mg tablets.

General

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.

When considering the use of methotrexate for chemotherapy, clinicians must evaluate the need and potential value of the drug against the risks, adverse effects or toxic effects. Most adverse effects are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved before commencing methotrexate treatment, and should remain under the physician's constant supervision. Close monitoring for toxicity throughout treatment is mandatory, particularly in high dose therapy or where drug elimination could be impaired (renal impairment, pleural effusion, ascites).

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician.

Particular attention is recommended for patients with renal impairment, as it may lead to renal failure.

Methotrexate exits slowly from the third-space compartments (e.g. pleural effusions or ascites) which results in a prolonged terminal phase half-life and unexpected toxicity. In patients with significant third-space accumulation, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels. Such patients require especially careful monitoring for toxicity, and require dose reduction, or in some cases, discontinuation of methotrexate administration (see Section 4.4 Special warnings and precautions for use: Pulmonary).

Deaths have been reported with use of methotrexate in the treatment of malignancy and psoriasis.

In the treatment of psoriasis, methotrexate should be restricted to severe, recalcitrant, disabling disease, which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after appropriate consultation.

Methotrexate should be used with extreme caution in the presence of debility and in extreme youth or age (see Section 4.2 Dose and method of administration, Elderly and Section 4.2 Dose and method of administration, Paediatric population).

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 Use in pregnancy).

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 Use in pregnancy).

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

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 Use in pregnancy).

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.

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 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 Interactions with other medicines and other forms of interactions), 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.

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 Overdose.

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.

Folinic acid deficiency

Folinic acid deficiency states may increase methotrexate toxicity.

Before taking a folate supplement, it is advisable to check vitamin B_{12} levels, since folate administration can mask symptoms of vitamin B_{12} 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 (see Section 4.5 Interactions with other medicines and other forms of interactions).

Organ system toxicity

Gastrointestinal

Gastrointestinal disorders frequently require dosage adjustment. Vomiting, diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Supportive therapy (including preventative dehydration) should be instituted.

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.

Haematologic

Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, pancytopenia, leukopenia, thrombocytopenia and bleeding. Leukocytes and neutrophils may occasionally show two depressions, the first occurring in 4-7 days and a second nadir after 12-21 days, followed by recovery. Clinical sequelae such as fever, infections, and haemorrhage from various sites and septicaemia may be expected.

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

In patients with malignant disease who have pre-existing bone marrow aplasia, leukopenia, thrombocytopenia or anaemia, the drug should be used with caution, if at all.

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 institution of appropriate therapy.

If profound leukopenia 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 Interactions with other medicines and other forms of interactions: Antibiotics -Oral antibiotics).

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

Hepatic

Methotrexate should not be used in patients who have a significant liver disease, particularly if this is/was alcohol-related (see Section 4.3 Contraindications).

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 liver enzyme elevations 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, and/or significant decreases of serum albumin may be indicators of serious liver toxicity and require evaluation. Liver biopsy after sustained use often shows histological changes. 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.

Particular attention should be given to the appearance of liver toxicity, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. It is imperative that liver function be determined prior to initiation of treatment and monitored regularly throughout therapy (see Section 4.4 Special warnings and precautions for use: Laboratory test monitoring of patients, Liver function tests/liver biopsy in this section). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

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. Secondary risk factors 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 treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided (see Section 4.5 Interactions with other medicines and other forms of interactions).

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.

Although liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity, it is imperative that hepatic function be determined, by liver function tests, prior to initiation of treatment and monitored regularly throughout therapy (see section 4.4 Special warnings and precautions for use).

Treatment should not be instituted or should be discontinued if any abnormalities of liver function tests or liver biopsy 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 twice or three times of the upper limit of normal 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 taken into consideration. Closer monitoring of liver enzymes is necessary especially in patients taking other hepatotoxic or haematotoxic medicinal products (e.g. leflunomide).

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.

Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population.

More frequent check-ups of liver function may become 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).

Musculoskeletal

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

Infection or immunologic states

Any infections should be attended to before initiation of methotrexate therapy. Methotrexate should be used with extreme caution in the presence of active infections, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Methotrexate therapy has immunosuppressive activity which can potentially lead to serious or even fatal infections. 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. Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy. 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, tuberculosis, hepatitis B or C) because of their potential activation.

Signs/symptoms of infection should be carefully observed and aggressive antibiotic therapy may be necessary.

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

Methotrexate has some immunosuppressive activity and immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is contraindicated during therapy (see Section 4.3 Contraindications). There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy (see Section 4.5 Interactions with other medicines and other forms of interactions).

Pulmonary

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 to develop 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. This lesion can occur at all dosages. Infection (including pneumonia) needs to be excluded.

Pulmonary function tests may be useful if lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available (see Organ system toxicity - Pulmonary in this section).

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 occur at any time during therapy and may not be fully reversible.

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 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.

Neurotoxicity

Systemic high-doses of methotrexate may cause significant CNS toxicity: patients should be closely monitored for neurologic signs/symptoms. If such manifestations occur the treatment should be discontinued and appropriate therapy instituted.

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

A transient acute neurologic syndrome has been observed in patients treated with high dosing regimens. Manifestations of this neurologic syndrome may include behavioural abnormalities, focal sensorimotor signs, including transient blindness, and abnormal reflexes. The exact cause is unknown.

Renal

Methotrexate is contraindicated in patients with severe renal impairment (see Section 4.3 Contraindications).

Methotrexate is excreted principally by the kidneys. Risk of renal damage leading to acute renal failure is due primarily to the precipitation in the kidney of the unchanged drug and metabolite (7-hydroxy methotrexate). Renal function should be closely monitored before, during and after methotrexate therapy. Impaired renal function may result in methotrexate accumulation in toxic amount or even additional renal damage. Methotrexate therapy should be undertaken with caution in patients with renal impairment.

Drug dosage should be reduced or discontinued until renal function is improved or restored. High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules.

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 Interactions with other medicines or other forms of interactions) 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.

Skin

Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin ulceration/necrosis and erythema

multiforme have been reported in children and adults within days of methotrexate administration. Reactions were noted after single or multiple doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients and a few cases of anaphylactoid reactions have been reported. 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, people taking methotrexate 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.

Methotrexate level

Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g. pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function.

Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate folinic acid rescue is delayed for more than 42 to 48 hours.

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.

Use in hepatic impairment

Methotrexate should not be used in patients with severe hepatic impairment or in patients who have a significant liver disease, particularly if this is/was alcohol-related. See **WARNINGS** box and Section 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Use in renal impairment

Methotrexate should not be used in patients with severe renal impairment. See **WARNINGS** box and Section 4.3 Contraindications and 4.4 Special warnings and precautions for use.

Use in the 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 (see Section 4.2 Dose and method of administration).

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. See Section 4.2 Dose and method of administration.

Paediatric use

Methotrexate should be used with extreme caution in young children. Cases of overdose by miscalculation of dosage have occurred particularly in juveniles. See Section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

Information for patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic 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 Dose and method of administration). The prescriber should specify the day of intake on the prescription. Pharmacists should clearly indicate the day of the week the weekly dose is to be taken on the dispensing label. Patients should be aware of the 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 a persistent cough or dyspnoea.

Patients should be advised to contact their doctor immediately if they experience symptoms of spitting or coughing up blood.

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

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).

Patients should be advised that adverse reactions to methotrexate, such as dizziness and fatigue, may affect their ability to drive or operate machinery.

Chexate tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The content of lactose (see Sections 2 Qualitative and quantitative composition and 4.2 Dose and method of administration) should be taken into account if high doses are administered to patients with diabetes mellitus.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Chemotherapeutic agents

Enhancement of nephrotoxicity may be seen if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

L-Asparaginase

The administration of L-asparaginase has been reported to antagonise the effect of methotrexate.

Mercaptopurine

Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require a dose adjustment.

Drugs highly bound to plasma proteins

Methotrexate is bound in part to serum albumin after absorption and toxicity may be increased because of displacement by other highly bound drugs such as salicylates, sulphonamides, sulphonylureas, phenylbutazone, phenytoin, and some antibacterials such as penicillins, tetracycline, chloramphenicol, pristinamycin, probenecid and para-aminobenzoic acid. When methotrexate is used concurrently with these drugs, its toxicity may be increased.

Hypolipidaemic compounds

Hypolipidaemic compounds such as cholestyramine proved preferential binding substrates compared to serum proteins when given in combination with methotrexate. These drugs, especially salicylates and sulphonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

Probenecid and drugs reducing tubular secretion

Since probenecid and weak organic acids, such as “loop-diuretics”, as well as pyrazoles reduce tubular secretion, great caution should be exercised when these medicinal products are co-administered with methotrexate.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs should not be administered prior to or concomitantly with high dose methotrexate, for example as used in the treatment of osteosarcoma. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe haematological (including bone marrow suppression and aplastic anaemia) and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Unexpectedly severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with NSAIDs including aspirin and other salicylates, azapropazone, diclofenac, indomethacin and ketoprofen. The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an inhibiting effect of NSAIDs on prostaglandin E2 synthesis yielding to a significant decrease of blood renal flow, resulting in reduced methotrexate excretion. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

Antibiotics

Ciprofloxacin

Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored.

Penicillins and sulfonamides

Penicillins and sulfonamides may reduce renal clearance of methotrexate, thereby increasing serum concentrations of methotrexate. Haematologic and gastrointestinal toxicity have been observed in combination with high and low dose methotrexate. Use of methotrexate with penicillins and sulfonamides should be carefully monitored.

Oral antibiotics

Reduced oral methotrexate absorption from the gastrointestinal tract has been seen in the presence of oral antibiotics. Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive anti-folate effect.

Concurrent use of the anti-protozoal pyrimethamine may increase the toxic effects of methotrexate because of an additive anti-folate effect.

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to methotrexate and should not be given concomitantly. Folate deficiency states may increase methotrexate toxicity.

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

Other cytotoxic drugs

Methotrexate is often used in combination with other cytotoxic drugs. Additive toxicity may be expected in chemotherapy regimens which combine drugs with similar pharmacologic effects and special monitoring should be made with regard to bone marrow depression, renal, gastrointestinal and pulmonary toxicity. The dosage of methotrexate should be adjusted if it is used in combination with other chemotherapeutic agents with overlapping toxicities.

Hepatotoxic agents

Concurrent use of other potentially hepatotoxic agents (e.g. leflunomide, sulfasalazine and alcohol) should be avoided due to an increased risk of hepatotoxicity. Special caution should be exercised when

azathioprine is given concurrently with methotrexate. The combination of methotrexate with retinoids, such as acitretin, is contraindicated (see Section 4.3 Contraindications).

Allopurinol

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

Leflunomide

Methotrexate in combination with leflunomide may also increase the risk of pancytopenia and interstitial pneumonitis.

Nitrous oxide anaesthesia

The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe unpredictable myelosuppression, stomatitis and neurotoxicity with intrathecal administration. Whilst this effect can be reduced by the use of folinic acid rescue (see Section 4.9 Overdose), avoid concomitant use of nitrous oxide in patients receiving methotrexate. Use caution when administering methotrexate after a recent history of nitrous oxide administration.

Amiodarone

Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerative skin lesions.

Psoralen plus ultraviolet light (PUVA) therapy

Skin cancer has been reported in a few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).

Packed red blood cells

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum-methotrexate concentrations.

Haematotoxic agents

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

Vaccines

Methotrexate is an immunosuppressant and may reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections and are therefore contraindicated (see Section 4.3 Contraindications).

Theophylline

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Diuretics

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

Proton pump inhibitors

Coadministration of proton pump inhibitors (PPIs) (e.g. omeprazole, pantoprazole) with methotrexate may decrease the clearance of methotrexate causing elevated methotrexate plasma levels with clinical signs and symptoms of methotrexate toxicity. Concomitant use of proton pump inhibitors and high dose methotrexate should therefore be avoided, especially in patients with renal impairment (see Section 4.4 Special warnings and precautions for use).

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 loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin is possible.

Ciclosporin and other immune-modulating agents

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

DMARDS (disease-modifying antirheumatic drugs)

The interactions of methotrexate and other antirheumatic drugs such as gold, penicillamine, hydroxychloroquine and sulfasalazine have not been studied. Concurrent use may increase the incidence of adverse effects.

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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 (see Use in pregnancy section below).

Use in pregnancy

Pregnancy Category D

Use of methotrexate is contraindicated throughout pregnancy (see Section 4.3 Contraindications).

Methotrexate causes embryotoxicity, abortion, intrauterine growth restriction and fetal defects in humans. Methotrexate has been shown to be teratogenic. It has caused fetal death and/or congenital abnormalities in humans; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be 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. pregnancy test prior to initiating therapy.

Both male and female patients should be fully counselled on the serious risk to the fetus should they become pregnant 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, although 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.

Teratogenicity

There is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremital malformations) and in several animal species.

Use in lactation

Methotrexate passes into breast milk and is contraindicated during breastfeeding (see Section 4.3 Contraindications). Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Central nervous system symptoms, such as fatigue and dizziness, can occur during treatment with methotrexate which may have minor or moderate influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity. See Section 4.4 Special warnings and precautions for use for specific reference to medically important and long term events including those following long term treatment or high cumulative doses (e.g. hepatic toxicity).

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. This includes use of folinic acid (calcium folinate) (see Section 4.4 Special warnings and precautions for use and 4.9 Overdose).

The most common adverse reactions of methotrexate are bone marrow suppression and mucosal damage which manifest as ulcerative stomatitis, leukopenia, thrombocytopenia, nausea and other gastrointestinal disorders. Other reported adverse reactions include malaise, undue fatigue, chills and fever, headache, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infections.

In general, the incidence and severity of side effects are related to dose, dosing frequency, method of administration and duration of exposure. Adverse reactions are most common when using high and repeated doses of methotrexate in the treatment of malignant neoplasms.

Adverse reactions as reported for the various organ systems are as follows:

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). *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, leukopenia, 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 disorders

Diabetes mellitus, metabolic disorder.

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 disorder, cranial nerve palsies, leukoencephalopathy, encephalopathy, CSF pressure increased, neurotoxicity, arachnoiditis, coma, paraplegia, stupor, ataxia, dementia, unusual cranial sensations, Guillain Barre Syndrome, hypoesthesia, meningism, paralysis, brain oedema.

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, non-infectious peritonitis, toxic megacolon, malabsorption, enteritis, changes 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 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 and bone disorders

Osteoporosis, osteonecrosis (aseptic necrosis of the femoral head), soft tissue necrosis, abnormal tissue cell changes, arthralgia/myalgia, 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, pyrexia, chills, malaise, fatigue, increased rheumatoid nodules, oedema, peripheral oedema, wound healing impairment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported (see **WARNINGS** box and Section 4.2 Dose and method of administration).

Signs and symptoms

Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. These signs and symptoms include leukopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding, anorexia, progressive weight loss and bloody diarrhoea. In some cases of overdose, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure and aplastic anaemia were also reported.

Recommended treatment

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

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.

In cases of massive overdose, hydration and urinary alkalinisation may be necessary to prevent the precipitation of the drug and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. However, effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialysator.

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

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antimetabolites, folic acid analogues

ATC code: L01BA01

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Methotrexate (4-amino-10 methyl folic acid) is an antimetabolite and an analogue of folic acid. The drug enters the cells via an active transport system for reduced folates and, due to a relatively irreversible binding, the drug inhibits the enzyme dihydrofolate reductase, which catalyses the reductive process of folic acid into tetrahydrofolic acid. The inhibited formation of tetrahydrofolates results in an interference with DNA synthesis, repair and cell replication. The affinity of dihydrofolate reductase for methotrexate is far greater than its affinity for folic acid or dihydrofolic acid and, therefore, even very large amounts of folic acid given simultaneously will not reverse the effects of methotrexate. The drug seems also to cause an increase in intracellular deoxyadenosine triphosphate, which is thought to inhibit ribonucleotide reduction and polynucleotide ligase, an enzyme concerned in DNA synthesis and repair.

Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, spermatogonia and cells of the urinary bladder are in general more sensitive to the pharmacological actions of methotrexate.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Low oral doses (up to 25 – 30 mg/m^2) are rapidly absorbed from the gastrointestinal tract but absorption at higher doses is erratic, possibly because of a saturation effect. Variability in methotrexate absorption

has been however detected in subjects receiving oral treatment due to drug-induced epithelial denudation, motility changes and alterations in intestinal flora. In addition, food has been shown to delay absorption and reduce peak concentration. Peak serum levels are reached within 1-5 hours following oral administration.

Distribution

Approximately 50% of absorbed methotrexate is reversibly bound to serum protein, but is easily diffused into body tissue cells, where the drug is actively transported across the cell membranes.

Methotrexate is widely distributed into body tissues with highest concentration in the kidneys, gall bladder, spleen, liver and skin. Small or insignificant amounts cross the blood-brain barrier and enter CSF following oral or parenteral administration; this may be increased when giving higher doses. Small amounts have been detected in saliva and breast milk. The drug crosses the placental barrier.

Methotrexate is retained for several weeks in the kidneys and for months in the liver, even after a single therapeutic dose. Sustained serum concentrations and tissue accumulation of methotrexate may result from repeated daily doses.

The drug enters slowly into third-space collections of fluid, such as pleural effusions, ascites and marked tissue oedemas.

Biotransformation

At low doses the drug does not appear to undergo significant metabolism; following high-dose therapy methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. A small amount of metabolism to the 7-hydroxy derivative may occur at doses commonly prescribed.

Before absorption, methotrexate may be partially metabolised by the intestinal flora to 2,4-diamino-N10-methylpteroic acid, a pharmacologically inactive metabolite.

Elimination

Clearance from plasma is reported to be triphasic: the first phase probably involves distribution into organs; the second renal excretion; and the third the methotrexate passage into the enterohepatic circulation.

The terminal half-life after low oral doses is in the range 3 to 10 hours. Total clearance averages 12 L/h, but there is wide interindividual variation, delayed drug clearance having been identified as one of the major factors responsible for drug toxicity.

Excretion is mainly through the kidneys via glomerular filtration and active transport. The pattern of elimination, however, varies considerably according to the dosage. Methotrexate excretion is impaired and accumulation occurs more rapidly in patients with impaired renal function. In addition, simultaneous administration of weak organic acids such as salicylates may suppress methotrexate clearance. The drug is slowly released from third-space compartments, giving prolongation of plasma disappearance and increased risk of toxicity.

5.3 PRECLINICAL SAFETY DATA

The intraperitoneal LD50 of methotrexate was 94 and 6-12 mg/kg for mice and rats, respectively. The oral LD50 of the compound in rats was 180 mg/kg. The tolerance to methotrexate in mice increased

with age. In dogs, the intravenous dose of 50 mg/kg was lethal. The main targets after a single dose were the haemolymphopoietic system and G.I. tract.

The toxic effects after repeated administration of methotrexate were investigated in mice and rats. The main targets of methotrexate in the above animal species were the haemolymphopoietic system, G.I. tract, lung, liver, kidney, testes and skin. The tolerance of mice to chronic methotrexate doses increased with age.

Genotoxicity

Methotrexate is mutagenic *in vivo* and *in vitro*. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells. The clinical significance of these findings is uncertain.

Carcinogenicity

No controlled human data exist regarding the risk of neoplasia with methotrexate.

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results.

Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome have been documented in patients treated with methotrexate.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires initiation of cytotoxic therapy.

Benefit should be weighed against this potential risk before using methotrexate alone or in combination with other drugs, especially in children or young adults.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate

6.2 INCOMPATIBILITIES

Methotrexate is incompatible with cytarabine, fluorouracil and prednisolone.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C. Keep the blisters in the outer carton, in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

White, opaque PVC/Al blister pack.

Chexate 2.5 mg: 24 and 30 tablets.

Chexate 10 mg: 10 and 50 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects.

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

Pregnant staff should be excluded from working with this drug.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Orion Pharma (NZ) Limited
c/o Max Health Limited
PO Box 44452
Pt Chevalier, Auckland 1246
Telephone: (09) 815 2664

9 DATE OF FIRST APPROVAL

27 November 2024

10 DATE OF REVISION

2 October 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
General	Revision to Boxed warning
4.1	Addition of Rheumatois arthritis indication
4.2	Update to dosing and administration
4.3	Deletion of contraindications and list consolidation
4.4	Update to multiple sections within Special warnings and precautions for use

4.5	Information added on administration with additional haematotoxic products
4.6	Update to Effect on fertility and Use in pregnancy
4.8	Inclusion of adverse events under Nervous system disorders, Cardia disorders, Gastrointestinal disorders and General disorders and administration site conditions, revised website address for reporting adverse events
4.9	Deletion of calcium folinate dosing instructions with reference to calcium folinate prescribing information, modified statement as per format requirements