NEW ZEALAND DATA SHEET – DBL™ METHOTREXATE INJECTION

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.

Use only isotonic and preservative-free methotrexate for intrathecal administration. For more information, see section 2 Qualitative and Quantitative Composition, section 3 Pharmaceutical Form and section 4.2 Dose and Method of Administration.

1. PRODUCT NAME

DBL Methotrexate Injection (methotrexate) 100 mg/mL solution for injection

DBL Methotrexate Injection (methotrexate) 5 mg/2 mL solution for injection

DBL Methotrexate Injection (methotrexate) 25 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DBL Methotrexate 100 mg/mL Injection contains methotrexate 100 mg.

Each mL of DBL Methotrexate 5 mg/2 mL Injection contains methotrexate 2.5 mg.

Each mL of DBL Methotrexate 25 mg/mL Injection contains methotrexate 25 mg.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Methotrexate Injection is a sterile solution. Sodium chloride is included for isotonicity except in the 100 mg/mL vial. DBL Methotrexate Injection is preservative-free.

DBL Methotrexate Injection has a pH of 7.5 to 9.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic chemotherapy

Methotrexate has a broad spectrum of antineoplastic activity. It is indicated for the treatment of breast cancer, gestational choriocarcinoma, and in patients with chorioadenoma destruens and hydatidiform mole.

Methotrexate may be used in combination with other chemotherapeutic agents for the palliative treatment of acute leukaemias, particularly acute lymphoblastic leukaemia. It may also be used in the treatment of Burkitt's lymphoma, advanced stages (III and IV, Peters' Staging System) of lymphosarcoma, especially in children, and in advanced cases of mycosis fungoides.

High dose therapy

In high-dose schedules, methotrexate may be effective alone or in combination therapy, in the treatment of epidermoid cancers of the head and neck, osteogenic sarcoma and bronchogenic carcinoma.

Calcium folinate (leucovorin calcium) must be used in conjunction with high dose methotrexate therapy.

Psoriasis chemotherapy (see WARNINGS box)

Methotrexate may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment in adults. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.

Rheumatoid arthritis chemotherapy (see WARNINGS box).

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

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

Dose

Methotrexate should only be prescribed by clinicians with experience in the use of methotrexate and a full understanding of the risks and benefits of methotrexate therapy.

(a) 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.

The dose of methotrexate is usually 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.

Trophoblastic neoplasms

Methotrexate is administered intramuscularly in doses of 15 mg to 30 mg daily for a five day course. A repeat course may be given after a period of one or more weeks provided all signs of toxicity have disappeared. Three to five courses of therapy are usually employed. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin hormone (CGH) which should return to normal or less than 50 IU/24 hours, usually after the 3rd or 4th course. Complete resolution of measurable lesions usually occur 4 to 6 weeks later. One to two courses of methotrexate after normalization of CGH are usually recommended. Before each course of methotrexate, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antineoplastic drugs has been reported as being useful.

Since hydatidiform mole may precede 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 trophoblastic neoplasms.

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. Methotrexate dosage was 40 mg/m^2 intravenously on the first and eighth days.

Leukaemia

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

Methotrexate in doses of 3.3 mg/m^2 orally in combination with prednisolone 60 mg/m^2 daily has been given for induction of remission of lymphoblastic leukaemia. When remission and general clinical improvement have been attained, a maintenance dosage of methotrexate 30 mg/m^2 IM twice weekly may be given. This treatment is expected to produce remission in 50% of patients treated, usually within 4 to 6 weeks.

Alternatively, 2.5 mg/kg IV every 14 days may be given. Should relapse occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen. A variety of dosage schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic agents have recently been introduced. Multiple drug

therapy with several agents, including methotrexate given concomitantly, appears to be gaining increasing support in both the acute and chronic forms of leukaemia.

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

Meningeal leukaemia

Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or remain silent and be diagnosed only by examination of the cerebrospinal fluid (CSF), which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of methotrexate from blood serum to the CSF is minimal, for adequate therapy the drug is administered intrathecally. Only preservative-free methotrexate should be used for intrathecal administration.

It is now common practice to administer methotrexate intrathecally as prophylaxis in all cases of acute lymphocytic leukaemia.

By intrathecal injection the distribution of methotrexate is in the CSF, the volume of which is dependent upon age and not body surface area. The CSF is at 40% of adult volume at birth and reaches adult volume in several years. The recommended dose by age is:

Age (yrs)	**less than 1**	**1**	**2**	**3+ older**
Dose (mg)	6	8	10	12

There is some indication that infants less than 4 months and adults 70 years of age or older may have increased acute toxicity with the doses recommended and dose reduction may be indicated.

For the treatment of meningeal leukaemia, intrathecal methotrexate may be given at intervals of 2 to 5 days, however there is some indication that doses given at intervals of less than one week may result in increased toxicity.

Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal, then one additional dose of the drug is administered.

For prophylaxis against meningeal leukaemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

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

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

Lymphomas

The usual dosage of methotrexate for the treatment of stage I or II of Burkitt's lymphoma is 10 to 25 mg per day orally for 4 to 8 days. In stage III methotrexate is commonly given concomitantly with other antineoplastic agents. In all stages, several courses of drug therapy are usually administered interposed with 7 to 10 day rest periods. Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily.

Methotrexate is of no value in the treatment of Hodgkin's Disease.

Mycosis fungoides

Initial dosage and dosage adjustment are determined by patient response and haematologic monitoring.

Methotrexate has also been given IM in doses of 50 mg once weekly or 25 mg twice weekly.

Methotrexate appears to produce clinical remissions in 50% of the cases treated.

High-dosage therapy (see section 4.4 Special Warnings and Precautions for Use)

Recent published literature should be consulted for details. Dosage regimens have varied considerably in different studies depending upon the nature and severity of the disease, the experience of the investigator etc. It must be emphasised that high dosages should be only used by qualified specialists and in hospitals where the necessary facilities are available.

In order to prevent precipitation of methotrexate in the renal tubules, the patients should maintain an adequate urine flow by drinking plenty of fluids for 2 days after a high dose injection (greater than 200 mg),and keep the urine alkaline by using sodium bicarbonate continuously for at least 24 hours afterwards.

(b) Psoriasis chemotherapy

Recommended dose schedules for a 70 kg adult are:

The effective weekly dose is generally between 10 and 25 mg/week, IM or IV. Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed a maximum dose of 25 mg/week. After optimal response has been achieved, each dosage schedule should be reduced to the lowest possible dose.

(c) Rheumatoid arthritis chemotherapy

The recommended starting dose is 7.5 mg parenterally (e.g IM) once weekly. Therapeutic response usually begins within three to six weeks and the patient may continue to improve for another twelve weeks or more. The dosage in each schedule 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, but not ordinarily to exceed a total weekly dosage of 20 mg. Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible amount of drug and with the longest rest period.

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 three to six weeks.

Method of administration

(a) Antineoplastic chemotherapy

DBL Methotrexate Injection products suitable for IV, IM, intra-arterial or intrathecal use: DBL Methotrexate Injection (methotrexate) 5 mg/2 mL solution for injection DBL Methotrexate Injection (methotrexate) 25 mg/mL solution for injection **DBL Methotrexate Injection products suitable for IV use only. Not for intrathecal use as the solution is hypertonic:** DBL Methotrexate 100 mg/mL injection vial (Hypertonic)

A guideline of a ratio of 1:30 is given for the conversion of mg/kg body weight to mg/m^2 body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Psoriasis and rheumatoid arthritis chemotherapy

General

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

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

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. (Noting that toxic effects have been seen at all doses and can occur at any time during therapy.)

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 commonly used injectable dosage schedule is weekly parenteral intermittent large doses. All schedules should be continually tailored to the individual patient. A single test dose of 5 to 10 mg parenterally one week prior to initiation of therapy is recommended to detect any idiosyncratic reaction.

Important warning about the dosage of methotrexate

In the treatment of psoriasis and rheumatoid arthritis, methotrexate must only be taken once a week. Dosage errors in the use of methotrexate can results in serious adverse reactions, including death. Please read this section of the product information carefully.

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.

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 Population

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 Contraindications and 4.4 Special Warnings and Precautions for Use). 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 its established use in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis, the safety and efficacy of methotrexate in children has not been fully elucidated. Methotrexate is not recommended in paediatric patients (see section 4.4 Special Warnings and Precautions for Use).

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 Special Warnings and Precautions for Use).

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 Fertility, Pregnancy and Lactation)
- 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.
- Radiotherapy, to the central nervous system, should not be given concurrently with intrathecal methotrexate.

4.4 Special warnings and precautions for use (see Warnings box)

Weekly dosing in the treatment of rheumatoid arthritis, psoriasis

Both the clinician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen in psoriasis treatment, as mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see section 4.4 Special Warnings and Precautions for Use, section 4.2 Dose and Method of Administration; and section 4.9 Overdose). For the same reason great care should be taken with dispensing.

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

Precautions before starting treatment

General

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

The physician should be familiar with the various characteristics of the drug and its established clinical usage. The patient should be informed of the risks involved (including symptoms of toxicity), the need to seek medical attention promptly if toxicity occurs, and of the need for close follow-up and ongoing monitoring, including regular laboratory tests to monitor for toxicity.

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

Because of the possibility of serious toxic reactions (which can be fatal), methotrexate should be used only in neoplastic diseases (as indicated), or in patients with severe, recalcitrant, disabling psoriasis or rheumatoid arthritis that is not adequately responsive to other forms of therapy. The patient should be informed by the physician of the risks involved and should be under a physician's constant supervision.

Methotrexate has a high potential for toxicity, which is usually dose-related. The physician should be familiar with the various characteristics of the drug and its established clinical usage. Because the toxic effects can occur at any time during methotrexate therapy, patients **must** be kept under appropriate supervision so that signs or symptoms of possible toxicity or adverse effects may be detected as early as possible. This is especially important in patients undergoing high dose therapy or in those where drug elimination could be impaired (renal impairment, pleural effusion, ascites).

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 dosage should be reduced or drug discontinued and appropriate corrective measures taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyser. Caution should be exercised when reinstituting methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the doctor 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 (e.g., renal impairment, pleural effusion, ascites).

Fertility

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 effects on reproduction should be discussed with both male and female patients prior to initiating methotrexate (see section 4.6 Fertility, Pregnancy and Lactation).

Pregnancy

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 Fertility, Pregnancy and Lactation).

Pregnancy should be avoided if either partner is receiving methotrexate, during and after cessation of therapy. Reliable contraception is recommended during and for at least three months after the end of the treatment for males. For females, reliable contraception is recommended during and for at least six months after end of the treatment. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy, has not been clearly established.

See section 4.6 Fertility, Pregnancy and Lactation.

Use in lactation

Women should be advised not to breastfeed while being treated with methotrexate.

See section 4.6 Fertility, Pregnancy and Lactation.

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 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.

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 Interaction with Other Medicines and other Forms of Interaction), 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.

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.

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 Contraindications).

Pretreatment 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 stoppage of the drug 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/sulfamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances (see section 4.5 Interaction with Other Medicines and Other form of Interaction, Antibiotics, Oral antibiotics).

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

Gastrointestinal

Vomiting, diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur. 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.

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.

If vomiting, diarrhoea, stomatitis or other suggestive symptoms occur, interruption of treatment is generally required until symptoms cease and supportive therapy (including preventing dehydration) should be instituted until recovery occurs.

Gastrointestinal disorders frequently require dosage adjustment.

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

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. 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 tumours, 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.

Renal

Methotrexate is contraindicated in patients with severe renal impairment (see section 4.3 Contraindications). Caution and use of lower doses are recommended in renal impairment (see section 4.2 Dose and Method of Administration).

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 treatment. Impaired renal function may result in methotrexate accumulation in toxic amount or even additional renal damage.

If serum creatinine is increased, drug dosage should be reduced or discontinued until renal 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.

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment (see section 4.5 Interaction with Other Medicines and Other Forms of Interaction).

Hepatic

Methotrexate is contraindicated in severe hepatic impairment, particularly if alcohol related (see section 4.3 Contraindications). 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. It is imperative that liver function 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 and the consumption of alcohol should be avoided (see section 4.5 Interaction with Other Medicines and Other Form of Interaction).

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, 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 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.

Musculoskeletal

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

Infection or immunologic states

Methotrexate therapy has immunosuppressive activity, which can potentially lead to serious or even fatal infections.

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 (see section 4.3 Contraindications).

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.

Signs/symptoms of infection should be carefully observed. Patients should be advised to report all symptoms or signs suggestive of infection. Methotrexate treatment is generally interrupted in severe, acute or chronic infections and antibiotics given if necessary.

Immunisation

Immunisation may be ineffective when given during methotrexate therapy. 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 and section 4.5 Interaction with Other Medicines and Other Forms of Interaction).

Skin

Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's syndrome), and erythema multiforme have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of intramuscular, intravenous, or intrathecal administration. Recovery has been reported with discontinuation of therapy.

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.

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.

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

High dose therapy

Methotrexate has been used in very high dosage followed by leucovorin (calcium folinate) rescue in the treatment of certain neoplastic disease. It should not be attempted outside of

facilities where the necessary expertise and resources have been assembled. The recent published literature and local guidelines should be consulted.

Large doses should not be used in patients with impaired renal function or a third-space reservoir such as ascites or large pleural effusion. Renal function and serum levels should be carefully monitored in order to reveal potential toxicity. Administration of calcium folinate is mandatory in high-dose methotrexate therapy. The administration of calcium folinate, hydration and alkalinisation of the urine should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate in order to prevent renal precipitation in acidic urine.

Systemic high doses or intrathecal administration of methotrexate may cause significant CNS toxicity. Patients should be closely monitored for neurologic symptoms and if these occur treatment should be discontinued and appropriate therapy instituted. Transient acute neurologic syndrome has been observed in patients treated with high dose regimens of methotrexate. Manifestations of this neurologic syndrome may include behavioural abnormalities, focal sensorimotor signs, including transient blindness and abnormal reflexes. The exact cause is unknown.

Neurologic

There have been reports of leucoencephalopathy following IV administration of methotrexate in high doses to patients who have had craniospinal irradiation. Symptomatic patients were commonly noted to have leukoencephalopathy, encephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leucoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with folinic acid rescue even without cranial irradiation.

Discontinuation of methotrexate does not always result in complete recovery.

After the intrathecal or high dose use of methotrexate, the central nervous system toxicity which may occur can be classified as follows:

1. acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity and fever;

2. sub-acute myelopathy usually transient, characterised by e.g. paraparesis/ paraplegia and increased CSF pressure associated with involvement with one or more spinal nerve roots;

3. a delayed syndrome occurring months to years after treatment characterised by necrotising leucoencephalopathy and manifested by confusion, irritability, somnolence, ataxia, dementia, occasionally convulsions and, rarely, death. The effects are dose-related and occur particularly when intrathecal methotrexate is given at doses greater than 50 mg in combination with cranial irradiation and systemic methotrexate therapy.

Central nervous system toxicity can be progressive and even fatal. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leucoencephalopathy. Signs of neurotoxicity (meningeal irritation, transient or permanent paresis, encephalopathy) should be monitored following intrathecal administration of methotrexate.

Intrathecal and intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

There have been reports of patients with periventricular CNS lymphoma who developed cerebral herniation with the administration of intrathecal methotrexate.

Cases of severe neurological adverse reactions ranging from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given intrathecal methotrexate in combination with intravenous cytarabine. (see section 4.5 Interaction with Other Medicine and Other Forms of Interaction).

Since cases of encephalopathy/leucoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out for patients with non-cancer indications. Patients should be closely monitored for neurological symptoms, and if these occur treatment should be discontinued and appropriate therapy instituted.

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.

Monitoring of methotrexate concentrations should include determination of a methotrexate level at 24, 48, or 72 hours, and assessment of the rate of decline in methotrexate concentrations (to determine how long to continue folinic acid rescue).

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.

Paediatric use

Serious neurotoxicity, frequently manifested as generalised or focal seizures, has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 gram/m^2).

Safety and effectiveness in paediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Overdose by intravenous and intrathecal miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see section 4.2 Dose and Method of Administration).

Use in the 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.

Effects on laboratory tests

No data available.

Instructions to patients

1. 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.

2. 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. Baseline assessment should include a complete blood count with differential and platelet counts; hepatic enzymes; hepatitis B or C infection testing, renal function tests; and a chest X-ray.

3. 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).

4. 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 importance of adhering to the once weekly intake and that daily administration can lead to serious toxic effects.

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

6. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

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

4.5 Interaction with other medicines and other forms of interaction

Drugs highly bound to plasma proteins

As methotrexate is partly bound to serum proteins, its toxicity may be increased as a result of displacement by certain drugs such as salicylates, phenylbutazone, sulphonamides, sulphonylureas, phenytoin, para-aminobenzoic acid, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

Antibiotics

Ciprofloxacin

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

Oral antibiotics

Oral antibiotics such as tetracycline, chloramphenicol and nonabsorbable 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 additive antifolate effect.

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

Penicillins and sulfonamides

Penicillins and sulfonamides may reduce the renal clearance of methotrexate; haematologic and gastrointestinal toxicity has been observed in combination with high- and low- dose methotrexate. Use of methotrexate with penicillins and sulfonamides should be carefully monitored.

Hypolipidaemic compounds

Hypolipidaemic compounds such as cholestyramine provided preferential binding sites compared to serum proteins when given in combination with methotrexate. This may lead to decreased methotrexate serum levels.

Medicinal products that cause folic acid deficiency

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

Vitamins

In non-oncology conditions such as rheumatoid arthritis or psoriasis, 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 conditions other than arthritis, including in the treatment of neoplastic disease.

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

Disease-modifying antirheumatic drug (DMARD) and Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Oncology indications: 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. These unexpectedly severe toxicities have been reported with concomitant administration of methotrexate and aspirin, other salicylates, asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

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

Non-oncology indications: In treating rheumatoid arthritis with methotrexate, aspirin, NSAIDs, and/or low dose steroids may be continued. Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and the larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, has not been studied and may increase the incidence of adverse effects.

Probenecid

Renal tubular transport is diminished by probenecid; use of methotrexate with this drug should be carefully monitored. Probenecid may increase the methotrexate plasma half-life and thereby increase blood levels.

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 pnemonitis.

Chemotherapeutic agents

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent, e.g., cisplatin.

Cytarabine

Intrathecal methotrexate given concomitantly with IV cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke like episodes.

Mercaptopurine

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

L-asparaginase

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

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 performed 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.

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.

Hepatotoxic agents

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

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.

Theophylline

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

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 (methoxsalen 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.

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).

Proton pump inhibitors

A potential interaction may exist between methotrexate and proton pump inhibitors (e.g., omeprazole, pantoprazole).

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.

Concomitant use of PPIs and high dose methotrexate should therefore be avoided, especially in patients with renal impairment.

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.

Immunomodulatory agents

Particularly in the case of orthopaedic surgery where the risk of infection is high, combination therapy with methotrexate and immunomodulatory medicinal products must be used with caution.

Ciclosporin

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

4.6 Fertility, pregnancy and lactation

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.

Pregnancy – Australian Pregnancy Category D

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 has been detected in human breast milk and is contraindicated during breastfeeding. Women should be advised not to breast feed while being treated with methotrexate.

4.7 Effects on ability to drive and use machinery

Adverse reactions to methotrexate, such as dizziness and fatigue may affect the ability to drive or operate machinery.

4.8 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.

Ulcerative stomatitis, leucopenia, nausea and abdominal distress are the most common adverse effects. Others reported include malaise, undue fatigue, chills and fever, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection. The incidence and severity of side effects generally appear to be dose- and frequency-related. Adverse effects have been reported for the various systems.

System Organ Class (SOC)	Adverse Reactions
Skin and subcutaneous tissue disorders	Dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes, nail hyperpigmentation, acute paronychia , drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Rarely, painful plaque erosions may appear. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, soft tissue necrosis and osteonecrosis have also been reported. Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme have been reported in children and adults within days of oral, intramuscular, intravenous or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.
Blood and lymphatic system	Bone marrow depression, leucopenia, neutropenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenia, anaemia (including aplastic anaemia), hypogammaglobulinaemia, decrease in serum albumin. Clinical sequelae such as fever, infections, haemorrhage from various sites, septicaemia, lymphadenopathy and lymphoproliferative disorders (including reversible) may be expected. Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.
Cardiac disorder	Pericarditis, vasculitis, pericardial effusion, pericardial tamponade, pulmonary oedema, hypotension and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolus) have been reported with methotrexate therapy.
Alimentary system	Mucositis (gingivitis, pharyngitis, stomatitis, glossitis), decreased appetite, anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melena, gastrointestinal ulceration and bleeding, intestinal perforation, non-infectious peritonitis, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, chronic fibrosis, hepatic cirrhosis, elevated liver enzymes, decreased

	serum albumin and hepatic failure. In rare cases, the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month of cessation of therapy, changes in sense of taste (metallic taste).
Urogenital system	Renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction, infertility, abortion, fetal defects, fetal death, severe nephropathy, vaginitis, vaginal discharge, vaginal bleeding, vaginal ulceration, gynaecomastia.
Pulmonary system	Interstitial pneumonitis, (including fatalities), pleural effusion , pleurisy , interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis, death. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxia, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar). Pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications.
Nervous system	Paraesthesia, encephalopathy/leucoencephalopathy, headaches, dizziness, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, cranial nerve disorder/palsies coma and brain oedema. Aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterisation. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressures have followed intrathecal administration. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation. Other side effects include: neurotoxicity, arachnoiditis, paraplegia, stupor, ataxia, dementia, motor dysfunction, depression, confusional state and irritability, hypoesthesia, meningism, paralysis.
Eye disorders	Conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology including transient blindness/vision loss have been reported in patients receiving methotrexate.
Ear and labyrinth disorders	Tinnitus.

Infections and infestations	There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis jirovecii* pneumonia was the most common infection. Other reported infections include pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes Zoster*, *H.simplex* hepatitis, disseminated *H.simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia, reactivation of hepatitis B infection, worsening of hepatitis C infection, respiratory tract infection, cutaneous bacterial infections.
General Disorders and Administration Site Conditions	Sudden death, nodule, pyrexia, chills, malaise, fatigue, oedema, peripheral oedema, injection site reactions, injection site necrosis, wound healing impairment.
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome, melanoma and non-melanoma skin cancer have been documented in patients treated with methotrexate.
Other	Other reactions related to or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporosis, osteonecrosis (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, back pain, nuchal rigidity, nodulosis, stress fractures, loss of libido and impotence have been reported. A few cases of anaphylactoid reactions have been reported.

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

Cases of overdose (sometimes fatal) due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported (see section 4.4 Special Warnings and Precautions for Use).

Signs and symptoms

Symptoms following injectable overdosage would be expected to produce effects, which are an extension of the pharmacological effects. The toxic reactions expected would include those listed under section 4.8.

Management

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. After an inadvertent overdosage of methotrexate, calcium folinate should be given as soon as possible and preferably started within 1 hour after the administration of methotrexate. As the time interval between methotrexate administration and folinic acid initiation increases, the effectiveness of folinic acid in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with folinic acid. Refer to the calcium folinate data sheet for dosing and administration information.

The above mentioned statements on calcium folinate dosage do not apply with high-dosage methotrexate therapy. The dosages of calcium folinate have varied in different studies and the published literature on high-dosage methotrexate should be consulted.

Concomitant hydration and alkalinisation of the urine with sodium bicarbonate is recommended to prevent precipitation of methotrexate or its metabolite in the renal tubules. Patients undergoing methotrexate therapy should be advised to increase fluid intake. 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. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyzer.

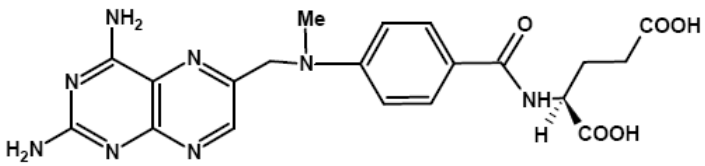
Patients who experience delayed early methotrexate elimination are likely to develop non reversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinisation, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent haemodialysis with a high-flux dialyzer may also be beneficial in these patients.

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

Chemical Structure



Chemical name: (2S)-2-[[4-[[(2,4-Diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid

Molecular weight: 454.4

CAS number

59-05-2

Mechanism of action

Methotrexate is an antimetabolite antineoplastic agent, which exerts its cytotoxic effect through competitive inhibition of dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolic acid results in interference with DNA synthesis and cellular reproduction.

Tissues with high rates of cellular proliferation, e.g., malignant cells, bone marrow, fetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are generally more sensitive to this effect of methotrexate.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in reproductive rates provides the basis for use of methotrexate to control the psoriatic process.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness) there is no evidence that it reduces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosion and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

5.2 Pharmacokinetic properties

Absorption

Peak serum levels may be achieved within 0.5 to 2 hours following intravenous (IV) or intramuscular (IM) administration.

Distribution

Approximately 50% of the absorbed methotrexate is reversibly bound to serum proteins. Methotrexate is widely distributed into body tissues and concentrates in the kidneys, liver and gastrointestinal tract. It also distributes into third-space accumulation of fluid, e.g., ascites or pleural effusions. Methotrexate does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) when given orally or parenterally. High concentrations of the drug, when needed, may be attained by intrathecal injection.

Biotransformation

Methotrexate does not appear to be appreciably metabolised.

Elimination

Methotrexate is predominantly excreted by the kidneys and small amounts appear in the faeces. Excretion of methotrexate is reduced in the presence of impaired renal function.

5.3 Preclinical safety data

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. *In vitro*, methotrexate caused chromosomal aberrations in Chinese hamster A(T1) C1-3 cells, induced morphological transformation in mouse C3H/10$T_{1/2}$ clone 8 cells and was associated with an increased incidence of large colony mutants at the tk locus in L5178Y/$tk^{\pm}$ mouse lymphoma cells. *In vivo*, it caused an increased incidence of polychromatic erythrocytes in mice and a transient and reversible increase in chromosomal aberrations in 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.

Reproductive and developmental toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

100 mg/mL:

Sodium hydroxide

Hydrochloric acid (as pH-adjustment agent)

Sodium hydroxide (as pH-adjustment agent)

Water for injections

5 mg/2 mL and 25 mg/mL:

Sodium chloride

Sodium hydroxide

Hydrochloric acid (as pH-adjustment agent)

Sodium hydroxide (as pH-adjustment agent)

Water for injections

6.2 Incompatibilities

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.

6.3 Shelf life

DBL Methotrexate Injection (methotrexate) 100 mg/mL: 30 months

DBL Methotrexate Injection (methotrexate) 5 mg/2 mL: 18 months

DBL Methotrexate Injection (methotrexate) 25 mg/mL: 24 months

DBL Methotrexate Injection, when diluted to a concentration of 1 mg/mL with sodium chloride 0.9% injection, glucose 5% injection, Hartmann's Injection, Ringer's Injection and 5% glucose in 0.9% sodium chloride injection, retains its potency for 24 hours when stored at room temperature in the presence and absence of fluorescent light.

However, because of microbiological contamination hazards, infusion of the admixed solutions should commence as soon as possible after preparation, and in any case, should be completed within 24 hours. Storage of admixed solutions should be at 2 to 8°C.

6.4 Special precautions for storage

Stored at or below 25°C and protected from light.

6.5 Nature and contents of container

DBL Methotrexate Injection (methotrexate) 100 mg/mL: Glass vial, 10 mL, 50 mL

DBL Methotrexate Injection (methotrexate) 5 mg/2 mL: Glass vial, 2 mL

DBL Methotrexate Injection (methotrexate) 25 mg/mL: Glass vial, 2 mL, 20 mL

6.6 Special precautions for disposal and other handling

Instructions for handling

The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good handling technique
- pregnant staff should be excluded from working with this drug
- personnel handling injectable methotrexate should wear protective clothing including goggles, gowns and disposable gloves and masks
- a designated area should be assigned for preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper
- all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution; medical attention should be sought.

The liquid vials are preservative-free and should therefore be used once only and discarded.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

DBL Methotrexate Injection (methotrexate) 100 mg/mL: 08 August 1986

DBL Methotrexate Injection (methotrexate) 5 mg/2 mL: 29 July 1982

DBL Methotrexate Injection (methotrexate) 25 mg/mL: 22 September 1994

10. DATE OF REVISION OF THE TEXT

12 November 2024

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Summary table of changes

Section changed	Summary of new information
All	Minor editorial updates
Warnings Box	Abbreviation of information in warnings box for clarity.
4.1	Simplification of wording of rheumatoid arthritis indication. Addition of 'adults' age group to indication for psoriasis.
4.2	Review, rewording and update of information related to dose and method of administration for clarity, relevance and duplication. Update of information related to oncology use. Reduction of maximum weekly dose to 25 mg. Addition of information on starting dose and route of administration for rheumatoid arthritis. Addition of information on importance of weekly dosing. Addition of information on use in special populations.
4.3	Reformat of contraindications to list and change to listing irrespective of indication for use.
4.4	Review, rewording and update of information related special warnings and precautions for use.
4.5	Addition of information on interactions with medicinal products that cause folic acid deficiency, haematotoxic reagents and immunomodulatory agents.
4.6	Review and rewording of information related to fertility and pregnancy. Addition of intrauterine growth restriction.
4.8	Undesirable effects changed to tabular form. Addition of wound healing impairment, meningism, paralysis, changes in sense of taste (metallic) to list of undesirable effects. Update of adverse event reporting link.
4.9	Review and rewording of information related to overdose.