NEW ZEALAND DATA SHEET

WARNINGS

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

The patient should be fully informed of the risk of fatal or severe toxic reactions involved with the administration of methotrexate and should be under constant supervision of the physician.

Deaths have been reported with the use of methotrexate.

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

1. Methotrexate may produce marked depression of the bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.

2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastro-intestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of methotrexate with other drugs with hepatotoxic potential or alcohol should be avoided.

3. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

4. Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy.

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

6. Unexpectedly Serious adverse effects including severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with nonsteroidal anti-inflammatory drugs (NSAIDs).

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

8. Pulmonary toxicity including acute or chronic pneumonitis and pulmonary fibrosis, which can progress rapidly and is potentially fatal, has been associated with methotrexate therapy. It may occur acutely at any time during therapy and has been reported at low doses. Methotrexate should be discontinued and careful clinical evaluation be performed in patients developing symptoms of pulmonary toxicity (e.g., dry, non-productive cough, dyspnoea). Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded in patients presenting with symptoms of pulmonary toxicity. Management of Methotrexate induced pulmonary toxicity is mainly supportive. Methotrexate induced pulmonary toxicity may not be fully reversible. Patients should be closely monitored for pulmonary symptoms.

9. Methotrexate has been used in high-dosage schedules followed by calcium folinate (leucovorin calcium) in the adjuvant treatment of certain neoplastic diseases. This procedure is complicated and hazardous. It should not be attempted except by highly experienced teams following carefully designed protocols. The recent published literature should always be consulted.

10. **Impaired renal function**
    Methotrexate is usually contraindicated in patients with impaired renal function.

11. **Use in pregnancy** (Australia Pregnancy Category D)
    Methotrexate has caused fetal death and/or congenital anomalies. It should not be used in pregnant women or in those who might become pregnant unless the potential benefits can be expected to outweigh the considered risks. Methotrexate is contraindicated in the treatment of psoriasis and rheumatoid arthritis in pregnant women. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

    Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 3 months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

12. **Use in lactation**
    Women should be advised not to breastfeed while being treated with methotrexate.

13. **Use in children**
    Aside from its established use in cancer chemotherapy; the safety and efficacy of using methotrexate in children has not been fully elucidated.

14. 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 – Method of administration for more information.

15. Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity.

1. PRODUCT NAME

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

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

Methotrexate onco-vial injection (methotrexate) 25 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Each mL vial of Methotrexate Onco-Vial Injection contains methotrexate 25 mg.

For the full list of excipients, see section 6.1.

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 WARNING 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. 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)

Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.

Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

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

(a) Antineoplastic chemotherapy

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)

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:

Weekly single dose schedule: 10 to 25 mg IM or IV per week until adequate response is achieved. Weekly dosage should not exceed 50 mg.Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal response has been achieved, each dosage schedule should be reduced to the lowest possible dose with the largest possible rest period. Conventional topical therapy should be resumed as soon as possible.

(c) Rheumatoid arthritis chemotherapy

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
Methotrexate onco-vial 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.

(b) Psoriasis chemotherapy

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

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

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.

(c) Rheumatoid arthritis chemotherapy

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

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physical examination and laboratory tests before beginning, periodically during and before reinstituting methotrexate therapy. Appropriate steps should be taken in men and women to avoid conception during methotrexate therapy.

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.

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

Caution

Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Pharmacists should dispense no more than a seven (7) day supply of the drug at one time. Refill of such prescriptions should be by direct order (written or oral) of the physician only.

4.3 Contraindications

- Methotrexate is contraindicated in patients with severe renal impairment.
- In the treatment of psoriasis and rheumatoid arthritis, methotrexate is contraindicated in pregnant women and in patients with poor nutritional status, bone marrow depression, hepatic disorders or in those with pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.
- Methotrexate is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndrome(s).

- Breast feeding is contraindicated in women taking methotrexate.

- Methotrexate is contraindicated in rheumatoid arthritis patients with active, infectious disease or psoriasis patients with serious infections, and in psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis. Methotrexate is contraindicated in psoriatic and rheumatoid arthritis patients suffering severe renal disorders, alcoholism or hepatic disorders including alcoholic liver disease or other chronic liver disease.

- Methotrexate is contraindicated in patients with a known hypersensitivity to it or to any of the excipients.

- Radiotherapy to the central nervous system should not be given concurrently with intrathecal methotrexate.

- An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate and acitretin is also contraindicated.

4.4 Special warnings and precautions for use

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

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 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.

Pretreatment and periodic haematologic evaluations are essential to the use of methotrexate in chemotherapy because of its haematopoietic suppressive effects, manifesting as anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood-cell count indicates immediate cessation of the drug and appropriate therapy. Methotrexate should be used with caution, if at all, in patients with malignant disease who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia, or anaemia.

If vomiting, diarrhoea or stomatitis occur, resulting in dehydration, methotrexate should be discontinued until recovery occurs.

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms. Methotrexate should be discontinued and careful clinical evaluation should be performed in patients developing pulmonary manifestations (especially a dry, non-productive cough). Although clinically variable, the

typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on X-ray; infection needs to be excluded. This lesion can occur at all dosages (see **WARNING** box). Infection (including pneumonia) needs to be excluded.

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.

The following laboratory tests should be carried out as part of the essential clinical evaluation and appropriate monitoring of patients on methotrexate therapy; complete haemogram; haematocrit; urinalysis; renal and liver function tests. A chest x-ray is recommended. The tests should be performed prior to, during and after therapy.

During therapy for psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, liver and renal function every one to three months. More frequent monitoring is usually indicated during antineoplastic therapy. It is important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed. Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

During therapy of rheumatoid arthritis and psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or change in dosing, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration) more frequent monitoring may also be indicated.

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age.

Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Like other cytotoxic drugs, methotrexate may induce “tumour lysis syndrome” in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Methotrexate exits slowly from the third-space compartments (e.g., pleural effusions or ascites). This 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.

Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Liver enzyme elevations are frequently seen. These are usually transient and asymptomatic and do not appear predictive of subsequent hepatic disease. 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. Periodic liver biopsies are usually recommended for psoriatic patients

who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

The risk of developing acute hepatitis and chronic hepatotoxicity in psoriatic patients seems to be correlated not only to the cumulative dose of methotrexate but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total cumulative dose of at least 1.5 grams.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at: 1) before start of therapy or shortly after initiation of therapy (2 – 4 months); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, methotrexate should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy has been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4 – 8 week intervals in patients receiving methotrexate for rheumatoid arthritis.

Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis). If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy, or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Methotrexate therapy has immunosuppressive activity, which can potentially lead to serious or even fatal infections. Bacterial infection may occur or be a threat if profound leucopenia occurs during therapy. In this instance, the drug should be discontinued and appropriate antibiotic therapy instituted. If severe bone marrow depression occurs, blood or platelet transfusions may be required.

Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pnemocystis carinii* pneumonia should be considered.

Immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy (see section 4.5).

Severe, occasionally fatal, skin reactions 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.

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.

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.

High dose therapy

Methotrexate has been used in very high dosage followed by leucovorin (calcium folinate) rescue in the experimental treatment of certain neoplastic disease. This procedure is investigational and hazardous. It should not be attempted outside of facilities where the necessary expertise and resources have been assembled. The recent published literature 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.

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 **WARNING** box).

Use in renal impairment

As methotrexate is excreted primarily by the kidney, its use in the presence of impaired renal function may lead to drug accumulation with resultant toxicity or even additional renal damage. The renal status of the patient should be determined prior to and periodically during methotrexate therapy. Caution should be exercised if significant renal impairment is present. Drug dosage should be reduced or discontinued until renal function is improved or restored.

The urine should be kept alkaline throughout therapy with methotrexate (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0).

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinisation, and measurement of serum methotrexate and renal function are recommended.

Use in hepatic impairment

Transient abnormalities of liver function tests (elevated transaminases) are observed frequently but persistent abnormalities and/or significant decreases in serum albumin may indicate serious liver toxicity and require evaluation. Liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity.

When to perform a liver biopsy in rheumatoid arthritis patients has not been established, either in terms of cumulative methotrexate dose or duration of therapy. There is a combined reported experience in 217 patients with rheumatoid arthritis with liver biopsy both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There were 64 (7%) cases of fibrosis and only one (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks. When methotrexate is discontinued, a “flare” of arthritis usually occurs within three to six weeks.

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.

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.

4.5 Interaction with other medicines and other forms of interaction

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, tetracyclines, chloramphenicol and para-aminobenzoic acid. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

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.

The excretion of methotrexate from the body can be markedly reduced by the concurrent use of penicillins and sulfonamides. There is a considerable risk of methotrexate toxicity. Use of methotrexate with penicillins and sulfonamides should be carefully monitored.

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.

In inflammatory arthritis, such as rheumatoid arthritis, 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.

Nonsteroid anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with high doses of methotrexate. NSAIDs elevate and prolong serum methotrexate levels, resulting in deaths from severe haematologic 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.

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.

Probenecid may increase the methotrexate plasma half-life and thereby increase blood levels.

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

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

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

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.

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.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim alone and sulfamethoxazole/ trimethoprim have been reported rarely to increase the toxic effects (e.g., bone marrow suppression) of methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Increased toxic effects (e.g., bone marrow suppression) have also been reported in patients receiving methotrexate and pyrimethamine.

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

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

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

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

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

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

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

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

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).

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.

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

4.6 Fertility, pregnancy and lactation

Fertility

Methotrexate may cause defective oogenesis and spermatogenesis. Therefore, in men and women of fertile age, steps should be taken to avoid conception during methotrexate therapy. The risk of genetic abnormalities may persist after discontinuing methotrexate therapy. Thus, it is advised that both men and women avoid intercourse leading to conception for an indefinite period (at least 12 weeks) after discontinuing methotrexate to ensure the re-establishment of normal germinal cells.

Pregnancy – Australian Pregnancy Category D

Methotrexate has caused fetal death and/or congenital abnormalities; 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. Pregnant psoriatic or rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate, during and for at least 12 weeks after cessation of therapy.

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.

Skin and subcutaneous tissue disorders: Dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes. Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Rarely, painful plaque erosions may appear. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. 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, 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 proliferative disorders 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, 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), anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melena, gastrointestinal ulceration and bleeding, intestinal perforation, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, or 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.

Urogenital system: Renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction, infertility, abortion, foetal defects, foetal death, severe nephropathy, vaginitis, vaginal discharge.

Pulmonary system: Interstitial pneumonitis, 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, 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: Headaches, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, and coma. Aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. 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. There have been reports of leucoencephalopathy following IV administration of methotrexate in high doses to patients who have had craniospinal irradiation. 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). Symptomatic patients were commonly noted to have leukoencephalopathy, encephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

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

1. 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.

Eye disorders: Conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology including transient blindness have been reported in patients receiving methotrexate.

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 carinii* 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.

Other: Other reactions related to or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporotic effects (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, nodulosis, stress fractures, loss of libido, impotence and even sudden death, have been reported.

Radiation dermatitis and sunburn may be "recalled". A few cases of anaphylactoid reactions have been reported.

Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome melanoma and non-melanoma skin cancer have been documented in patients treated with methotrexate.

Reporting of suspected adverse reactions

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

4.9 Overdose

Discontinue methotrexate at the first sign of ulceration or bleeding, diarrhoea or marked depression of the haematopoietic system.

Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, 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.

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.

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. In general, when overdosage is suspected, the dose of calcium folinate should be equal to or higher than the offending dose of methotrexate, and should be given as soon as possible, preferably within the first hour after which it is much less effective. Calcium folinate may be administered by IV infusion in doses of up to 75 mg within 12 hours, followed by 12 mg IM every 6 hours for 4 doses. When average

doses of methotrexate appear to have an adverse effect, 6 to 12 mg of calcium folinate may be given IM every 6 hours for 4 doses.

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.

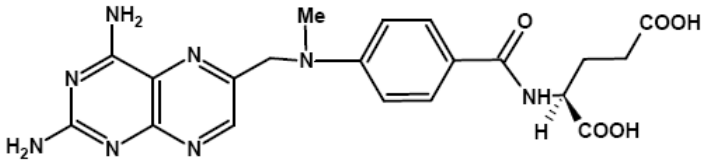
Patients who experience delayed early methotrexate elimination are likely to develop non reversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinisation, and close monitoring of fluid and electrolyte status, until 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 has been reported to cause chromosome damage.

Carcinogenicity

Methotrexate is considered to be carcinogenic. However, extensive epidemiologic studies are required to determine its carcinogenicity potential.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

100 mg/ml:

Sodium hydroxide

Water for injection

5 mg/2 mL and 25 mg/mL:

Sodium chloride

Sodium hydroxide

Water for injection

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

Methotrexate Onco-Vial 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

Methotrexate Onco-Vial 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

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

Methotrexate Onco-Vial Injection (Methotrexate) 25 mg/ml: 22 September 1994

10. DATE OF REVISION OF THE TEXT

8 December 2020

Summary table of changes

Section changed	**Summary of new information**
Warning Box	Editorial changes
4.2	Method of administration revised
4.8	Editorial changes