DBL™ Methotrexate Injection

WARNINGS

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

Patients 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 consultation.

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

2. At high or prolonged doses, methotrexate may be hepatotoxic. 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 liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential and 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 jirovecii* pneumonia, may occur with methotrexate therapy.

5. **Use in pregnancy**

   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 foetus should they become pregnant while undergoing treatment.

   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 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.

6. Methotrexate is usually contraindicated in patients with impaired renal function.

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

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

9. Pulmonary toxicity including acute or chronic interstitial pneumonitis (pneumonitis, pleural effusion) 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 and non-productive cough, dyspnoea). Management of methotrexate-induced pulmonary toxicity is mainly supportive. Methotrexate-induced pulmonary toxicity may not be fully reversible. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.

10. 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.

11. **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.

12. Use only isotonic and preservative-free methotrexate for intrathecal administration. For more information, see sections 2 Qualitative and quantitative composition, 3 Pharmaceutical form and 4.2 Dose and method of administration - Method of administration for more information.

13. 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.

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

15. **Use in lactation**

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

16. Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections.

1. NAME OF THE MEDICINE

Methotrexate BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Methotrexate Injection 5 mg/2 mL: Each 2 mL vial contains 5 mg methotrexate

DBL Methotrexate Injection 50 mg/2 mL: Each 2 mL vial contains 50 mg methotrexate

DBL Methotrexate Injection 500 mg/20 mL: Each 20 mL vial contains 500 mg methotrexate

DBL Methotrexate Injection 1 g/10 mL: Each 10 mL vial contains 1 g methotrexate

Sodium chloride is included for isotonicity except in the 1 g/10 mL vial.

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

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Methotrexate Injection is a clear yellow sterile solution of Methotrexate BP in Water for Injections BP.

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. 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.

Dosage

(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 normalisation 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 (intramuscular) 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 (intravenous) 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

Methotrexate has been given IM in doses of 50 mg once weekly or 25 mg twice weekly. Initial dosage and dosage adjustment are determined by patient response and haematologic monitoring.

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

(b) 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.

(c) 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.

Recommended dose schedules for a 70 kg adult

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.

(d) Rheumatoid arthritis chemotherapy

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

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 doctor 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.

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

DBL Methotrexate Injection products suitable for IV, IM, intra-arterial or intrathecal use:
DBL Methotrexate Injection 5 mg/2 mL
DBL Methotrexate Injection 50 mg/2 mL
DBL Methotrexate Injection 500 mg/20 mL

DBL Methotrexate Injection products suitable for IV use only. Not for intrathecal use as the solution is hypertonic:
DBL Methotrexate Injection 1 g/10 mL (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.

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.

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.

During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

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 [see WARNINGS box]

General

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

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.

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 should be used with extreme caution in the presence of 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.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see WARNINGS box).

Haematologic

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.

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.

Gastrointestinal

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

Pulmonary

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.

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms at each follow-up visit. 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 **WARNINGS** box). Infection (including pneumonia) needs to be excluded.

If methotrexate-induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Methotrexate-induced pulmonary toxicity may occur at any time during therapy and may not be fully reversible.

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

Laboratory test monitoring of patients

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.

Hepatic

Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Acutely, 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.

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 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.

Psoriasis

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.

Rheumatoid arthritis

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).

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. 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 jirovecii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia should be considered.

Immunisation

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

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.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8 Adverse effects (undesirable effects)). Periodic skin examination is recommended for all patients who are at increased risk for skin cancer. Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Exposure to intense sunlight or UV rays should be avoided unless medically indicated.

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.

Folinic acid deficiency

Folate deficiency states may increase methotrexate toxicity.

If acute methotrexate toxicity occurs, patients may require folinic acid. 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.

Before taking a folate supplement, it is advisable to check B12 levels, since folate administration can mask symptoms of B12 deficiency.

High dose therapy

Methotrexate has been used in very high dosage followed by leucovorin 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. 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 leukoencephalopathy 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 leukoencephalopathy 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, central nervous system toxicity may occur and 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 leukoencephalopathy 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 leukoencephalopathy. 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 Interactions with other medicines and other forms of interactions).

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

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 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 because impairment of renal function will decrease methotrexate elimination. 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.

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

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).

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.

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.

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).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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, probenecid and para-aminobenzoic acid, some antibiotics such as penicillins, tetracycline, pristinamycin and chloramphenicol. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

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.

Antibiotics

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

Penicillins and sulfonamides: Penicillins and sulfonamides may reduce the renal clearance of methotrexate; haematologic and gastrointestinal toxicity has been observed in combination with high- and low- dose methotrexate.

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.

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 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.

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.

Vitamins

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. Folate deficiency states may increase methotrexate toxicity.

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

Disease-modifying antirheumatic drug (DMARD) and Nonsteroidal anti-inflammatory drugs (NSAIDs)

Oncology indications: 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, azapropazone, 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.

Allopurinol

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

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.

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

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

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, avoid concomitant use of nitrous oxide in patients receiving methotrexate. Use with 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, retinoids, sulfasalazine and alcohol) should be closely monitored for possible increased risk of hepatotoxicity.

Theophylline

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

Diuretics

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

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.

Haematotoxic agents

Administration of additional haematotoxic medicinal products increases the likelihood of severe haematotoxic adverse reactions to methotrexate. Methotrexate in combination with leflunomide may increase the risk of pancytopenia and interstitial pneumonitis.

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 with 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.

Phenytoin

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

Ciclosporin

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

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

Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting the therapy. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

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

Use in pregnancy

In the treatment of psoriasis and rheumatoid arthritis, use of methotrexate is contraindicated throughout pregnancy (see section 4.3 Contraindications).

Methotrexate has been shown to be teratogenic. Methotrexate has caused embryotoxicity, abortion, fetal death 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 foetus if pregnancy occurs while undergoing treatment.

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.

Use in lactation

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 machines

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

4.8 Adverse effects (undesirable effects)

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

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: 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.

Cardiovascular system: 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, hepatotoxicity, periportal fibrosis, chronic fibrosis, hepatic cirrhosis, elevated liver enzymes, decreased serum albumin, increase of blood lactate dehydrogenase 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, 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.

Central nervous system: paraesthesia, encephalopathy/leukoencephalopathy, 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-Barré 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.

Ophthalmic: 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: 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 cytomegalovirus pneumonia, reactivation of hepatitis B infection, worsening of hepatitis C infection, respiratory tract infection, cutaneous bacterial infections.

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.

General disorders and administration site conditions: Sudden death, nodule, pyrexia, chills, malaise, fatigue, oedema, oedema peripheral, injection site reactions, injection site necrosis.

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, stomatitis, 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 Adverse effects (undesirable effects).

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 dialyser.

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 dialyser may also be beneficial in these patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

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

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 CSF when given orally or parenterally. High concentrations of the drug, when needed, may be attained by intrathecal injection.

Methotrexate does not appear to be appreciably metabolised. 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

Water for Injections BP

Sodium Chloride BP (except for 1 g/10 mL)

Sodium Hydroxide BP (as buffering agent and PH-adjustment agent)

Hydrochloric acid (as pH-adjustment agent)

6.2 Incompatibilities

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

6.3 Shelf life

Please refer to outer carton for expiration date.

6.4 Special precautions for storage

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

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.

Store below 25°C. Protect from light.

6.5 Nature and contents of container

DBL Methotrexate Injection is available in the following presentations:

DBL Methotrexate Injection 5 mg/2 mL clear glass vials, packs of 5.
DBL Methotrexate Injection 50 mg/2 mL clear glass vials, packs of 5.
DBL Methotrexate Injection 500 mg/20 mL clear glass vials, single packs.
DBL Methotrexate Injection 1 g/10 mL clear glass vials, single packs.

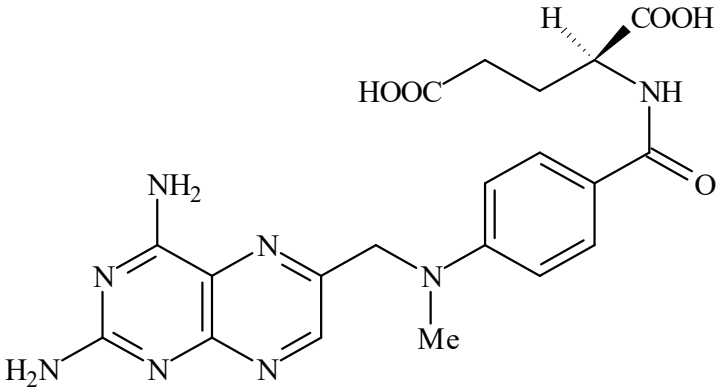
Not all presentations may be available locally.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Chemical name: (S)-2-[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino] benzoylamino] pentanedioic acid

Molecular formula: $C_{20}H_{22}N_8O_5$

Molecular weight: 454.4

CAS number

59-05-2

7. NAME AND ADDRESS OF MANUFACTURER

Hospira Australia Pty Ltd
1 – 5, 7 – 23 and 25 – 39 Lexia Place
Mulgrave, Victoria, 3170
Australia

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