

DBL® METHOTREXATE Injection BP

WARNINGS

Methotrexate must be used only by physicians experienced in antimetabolite 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, methotrexate should be restricted to severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after appropriate consultation.

1. Methotrexate may produce marked depression of 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 gastrointestinal 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 other drugs with hepatotoxic potential (including 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. Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections.
6. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.
7. Use in pregnancy: Pregnancy category D

Methotrexate has caused fetal death and/or congenital abnormalities. Therefore, it is not recommended in women of child-bearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic 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 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.

8. Impaired renal function is usually a contraindication.

9. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise, haemorrhage enteritis and death from intestinal perforation may occur.
10. Unexpectedly severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with nonsteroidal anti-inflammatory agents (NSAIDs).
11. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis and pleural effusion is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages. Infections (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.
12. Methotrexate has been used in very high-dosage followed by folinic acid (calcium folinate) rescue in the experimental treatment of certain neoplastic diseases. 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.
13. 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 Dosage and method of administration – Method of administration** for more information.
14. 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.
15. Use in lactation
Women should be advised not to breastfeed while being treated with methotrexate.
16. 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.

1. Name of the Medicine

Methotrexate

2. Qualitative and Quantitative Composition

Each vial of Methotrexate Injection BP contains Methotrexate 1000 mg/10 mL.

Methotrexate Injection BP 1000 mg in 10 mL is hypertonic. For the full list of excipients, see **Section 6.1 List of excipients**.

3. Pharmaceutical Form

Solution for injection.

Methotrexate Injection BP is a clear yellow-orange solution, free from visible particulates.

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 Dosage and method of administration

Dosage

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.

(a) Antineoplastic chemotherapy

Oral administration of methotrexate in tablet form is often preferred since absorption is rapid and effective serum levels are obtained. It is recommended that oral methotrexate should be taken on an empty stomach.

Methotrexate may be administered by intramuscular, intravenous, intra-arterial or intrathecal injection. Non-isotonic solutions of DBL® Methotrexate Injection should not be administered intrathecally.

A guideline of a ratio of 1:30 is given for the conversion of mg/kg body weight to mg/m² body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Trophoblastic neoplasms

The usual dosage is 15 to 30 mg daily orally or IM for 5 days. 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 occurs 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/m² 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/m² orally in combination with prednisolone 60 mg/m² 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/m² orally or 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 may 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 on 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 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

Dosage of methotrexate for the treatment of mycosis fungoides is usually 2.5 to 10 mg orally each day for weeks or months. 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

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

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.

There are three commonly used general types of dosage schedules:

- (1) weekly oral or parenteral intermittent large doses;
- (2) divided dose intermittent oral schedule over a 36-hour period;
- (3) daily oral with a rest period.

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 are:

- (1) Weekly single dose schedule: 10 to 25 mg orally, IM or IV per week until adequate response is achieved. Weekly dosage should not exceed 50 mg.
- (2) Divided dose schedule: 2.5 mg orally at 12-hour intervals for three doses or at 8 hour intervals for four doses each week. Weekly dosage should not exceed 30 mg.
- (3) Daily dose schedule: 2.5 mg orally daily for five days followed by a rest period of at least 2 days. Daily dosage should not exceed 6.25 mg.

Dosage in each schedule 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

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.

Recommended starting dosage schedules are single oral doses of 7.5 mg once weekly, or divided oral doses of 2.5 mg at twelve-hour intervals for three doses given as a course once weekly.

Therapeutic response usually begins within three to six weeks and the patient may continue to improve for another twelve weeks or more. The dosage in each schedule may be increased to 15 mg/week after six weeks in non-responsive patients. If necessary, dosage may be gradually increased further to achieve optimal response, but not ordinarily to exceed a total weekly dosage of 20 mg. Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible amount of drug and with the longest rest period.

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

Method of administration

DBL Methotrexate Injection product suitable for IV use only. Not for intrathecal use as the solution is hypertonic:

DBL METHOTREXATE 1 g/10 mL injection vial (Hypertonic)

Instructions for handling

As with all antineoplastic agents, trained personnel should prepare Methotrexate Injection BP. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling methotrexate. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as methotrexate.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare Methotrexate Injection BP, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

Single use only. Discard unused portion.

4.3 Contraindications

Methotrexate should not be given to:

- Patients with a known hypersensitivity to methotrexate or to any of the excipients.
- Pregnant women (see **Section 4.6 Fertility, pregnancy and lactation**).
- Breast-feeding women (see **Section 4.6 Fertility, pregnancy and lactation**).
- Patients with severe hepatic impairment.
- Patients with severe renal impairment.
- Patients with alcoholism or alcoholic liver disease.
- Patients who have overt or laboratory evidence of immunodeficiency syndromes.
- Patients with pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.
- Patients with severe acute or chronic infections.
- Psoriasis patients with peptic ulcer disease or ulcerative colitis.
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.
- An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate with retinoids, such as acitretin, is also contraindicated.
- Radiotherapy to the central nervous system should not be given concurrently with intrathecal

methotrexate.

4.4 Special warnings and precautions for use

Use with caution in the following circumstances

Methotrexate must be used only by physicians experienced in antimetabolite 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. Close monitoring for toxicity throughout treatment is mandatory, particularly in high dose therapy, or where drug elimination could be impaired (renal impairment, pleural effusion, ascites).

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

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

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

Methotrexate should be used with extreme caution in the presence of debility and in extreme youth or age (see Paediatric use and Use in the elderly).

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

Methotrexate, like other cytotoxic drugs, may trigger tumour lysis syndrome in patients with rapidly growing tumour.

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

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

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).

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

Folinic acid deficiency

Folate deficiency states may increase methotrexate toxicity.

Adequate folinic acid (calcium folinate) protection is indicated in high-dose methotrexate therapy. The administration of calcium folinate, hydration, and urine alkalinisation should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate. Appropriate calcium folinate administration can be discontinued when the serum methotrexate concentration level is below 10^{-8} M (see **Section 4.9 Overdose**).

If acute methotrexate toxicity occurs, patients may require folinic acid. In patients with 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 folinic acid rescue in the experimental treatment of certain neoplastic disease. High dosing regimens for other neoplastic diseases are investigational, hazardous and a therapeutic advantage has not been established. These procedures 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, because rapid drug excretion is important in limiting toxicity. Careful monitoring of renal function and methotrexate serum levels is required in order to reveal impending toxicity. Administration of calcium folinate is mandatory in high-dose methotrexate therapy. The administration of calcium folinate, hydration and urine alkalinisation should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate.

The use of methotrexate high-dose regimens (≥ 500 mg/m²) recommended for osteosarcoma requires meticulous care.

High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, using alkalinisation and measurement of serum methotrexate and creatinine levels are essential for safe administration.

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 (see **Section 4.9 Overdose**).

Organ system toxicity

Gastrointestinal

Methotrexate should be used with extreme caution in the presence of peptic ulcer and ulcerative

colitis. Methotrexate is contraindicated in psoriasis patients with peptic ulcer disease or ulcerative colitis (see **Section 4.3 Contraindications**).

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

In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Haematologic

Methotrexate may produce marked depression of bone marrow, and cause anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia, thrombocytopenia and bleeding. Clinical sequelae such as fever, infections, haemorrhage from various sites and septicaemia may be expected.

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

Pre-treatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of the common effects of haematopoietic suppression. These effects may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates that methotrexate should be immediately discontinued and appropriate therapy instituted.

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

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

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

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances (see **Section 4.5 Interactions with other medicines and other forms of interactions, Antibiotics, Oral antibiotics**).

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

Musculoskeletal

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

Infection or immunologic states

Any infections should be attended to before initiation of methotrexate therapy. Methotrexate should

be used with extreme caution in the presence of active infections, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Methotrexate therapy has immunosuppressive activity which can potentially lead to serious or even fatal infections. This factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

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

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.

Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential for re-activation.

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.

Immunisation

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

Neurologic

There have been reports of leucoencephalopathy following intravenous administration of methotrexate in high doses to patients who have had craniospinal irradiation (see Paediatric Use). Symptomatic patients were commonly noted to have leucoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

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

Discontinuation of methotrexate does not always result in complete recovery.

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

After intrathecal or high-dose use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: (1) acute chemical arachnoiditis manifested by such symptoms

as headache, back pain, nuchal rigidity, and fever; (2) sub-acute myelopathy, usually transient, characterised by e.g. paraparesis/paraplegia and increased CSF pressure associated with involvement with one or more spinal nerve roots; (3) a delayed syndrome occurring months to years after treatment characterised by chronic leucoencephalopathy and manifested by confusion, stupor, irritability, somnolence, ataxia, dementia, occasionally major convulsions, and coma. This central nervous system toxicity can be progressive and even fatal. 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. 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 that ranged 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, Cytarabine**).

Pulmonary

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

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

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

Patients should be closely monitored for pulmonary signs and symptoms at each follow-up visit. Methotrexate-induced pulmonary toxicity may occur at any time during therapy and may not be fully reversible.

Skin

Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin ulceration/necrosis and erythema multiforme have been reported in children and adults within days of methotrexate administration. Reactions were noted after single or multiple doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration

has been reported in psoriatic patients and a few cases of anaphylactoid reactions have been reported. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

Laboratory monitoring

In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate therapy: a complete blood count (with differential and platelet counts); haematocrit; urinalysis; renal function tests; hepatitis B or C infection testing; liver function tests; and a chest X-ray. The tests should be performed prior to therapy, at appropriate periods during therapy, and after termination of 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.

During therapy for psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, and hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. It may be important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed.

Pulmonary function tests

Pulmonary function tests may be useful if lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available (see **Section 4.4 Special warnings and precautions for use, Pulmonary**).

Methotrexate level

Monitoring methotrexate serum levels, adjusting dose and implementing rescue measures as appropriate can significantly reduce toxicity and mortality.

Patients with pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria or impaired renal function are predisposed to developing elevated or prolonged methotrexate levels. Therefore, routine monitoring of methotrexate levels should be carried out in these patients.

Delayed methotrexate clearance can also occur in the absence of these conditions.

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 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).

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 the following points: 1) before start of therapy or shortly after initiation of therapy (2 to 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 normally not a reason to avoid or discontinue methotrexate therapy, the drug should be used with

caution.

Information for patients

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

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

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

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

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

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

Use in hepatic impairment

Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported. With interruption of methotrexate therapy, abnormalities of liver function tests or liver biopsy should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

In the case of unresolving elevation of liver enzymes, a reduction of the dose or discontinuation of therapy should be considered. Closer monitoring of liver enzymes is necessary in patients taking other hepatotoxic or haematotoxic medicinal products (e.g. leflunomide).

Check liver function more frequently during initiation of methotrexate therapy, any time the dose is increased, and any time there is a risk of increased methotrexate exposure (e.g. dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as NSAIDs).

Liver biopsy after sustained use often shows histologic 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. The need for liver biopsy should be evaluated case by case and national recommendations should be followed. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment.

Methotrexate may cause acute and chronic hepatotoxicity, particularly at high dosage or with prolonged therapy, including liver atrophy, necrosis, hepatic cirrhosis, acute hepatitis, fatty changes and periportal fibrosis. Transient and asymptomatic liver enzyme elevations are frequently seen after methotrexate administration and are usually not a reason for modification of methotrexate therapy or predictive of subsequent hepatic disease.

Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity.

Particular attention should be given to the appearance of liver toxicity, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. It is imperative that liver function be determined prior to initiation of treatment and monitored regularly throughout therapy (see Laboratory monitoring). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

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

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

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

Use in renal impairment

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

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

Methotrexate is excreted principally by the kidneys. Renal function should be closely monitored before, during and after methotrexate therapy. Impaired renal function may result in methotrexate accumulation of toxic amounts or even additional renal damage. Methotrexate therapy should be undertaken with caution in patients with renal impairment.

Drug dosage should be reduced or discontinued until renal function is improved or restored. A high fluid throughput and alkalinisation of the urine to pH 6.5 – 7.0 throughout therapy with methotrexate is recommended as a preventative measure (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0).

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

and other forms of interactions).

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

Cases of overdose by miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see **Section 4.2 Dosage and method of administration**).

Serious neurotoxicity (often manifested by generalised or focal seizures) has been reported with unexpectedly high frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intravenous methotrexate (1 g/m²).

Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Chemotherapeutic agents

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

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 effect of methotrexate.

Mercaptopurine

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

Drug highly bound to plasma proteins

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

Hypolipidaemic compounds

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

Probenecid and drugs reducing tubular secretion

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

Non-steroidal anti-inflammatory drugs (NSAIDs)

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

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

Unexpectedly severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with NSAIDs, including aspirin and other salicylates, azapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

Antibiotics

Ciprofloxacin

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

Penicillins and sulfonamides

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

Oral antibiotics

Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive anti-folate effect.

Concurrent use of the anti-protozoal pyrimethamine may increase the toxic effects of methotrexate because of an additive anti-folate effect. Increased bone marrow suppression has been reported

in patients receiving methotrexate and pyrimethamine.

Vitamins

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

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

Other cytotoxic drugs

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

Hepatotoxic agents

Concurrent use of other potentially hepatotoxic agents (e.g. leflunomide, sulfasalazine and alcohol) should be avoided due to an increased risk of hepatotoxicity. Special caution should be exercised when azathioprine is given concurrently with methotrexate. The combination of methotrexate with retinoids, such as acitretin, is contraindicated (see **Section 4.3 Contraindications**).

Allopurinol

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

Leflunomide

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

Nitrous oxide anaesthesia

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

Amiodarone

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

Psoralen plus ultraviolet light (PUVA) therapy

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

Packed red blood cells

Care should be exercised whenever packed red blood cells and methotrexate are given

concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum-methotrexate concentrations.

Vaccines

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

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

Theophylline

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

Diuretics

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

Proton pump inhibitors

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

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

Use in pregnancy - Category D

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 fetus if pregnancy occurs whilst 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.

Teratogenicity

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

Use in lactation

Methotrexate passes into breast milk and is contraindicated during breastfeeding (see **Section 4.3 Contraindications**). The highest breast milk to plasma concentration ratio reached was 0.08:1. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

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

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

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

Immune system disorders: Anaphylactoid reaction, anaphylactic reaction, hypogammaglobulinaemia.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, painful erosion of psoriatic plaques, skin ulceration, skin necrosis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentation disorder (depigmentation/hyperpigmentation), alopecia, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail disorder, nail hyperpigmentation, acute paronychia.

Blood and lymphatic system disorders: Bone marrow failure, leucopenia, neutropenia, thrombocytopenia, anaemia, aplastic anaemia, megaloblastic anaemia, eosinophilia, pancytopenia, agranulocytosis, lymphadenopathy, lymphoproliferative disorders (including reversible), haemorrhage (from various sites), septicæmia.

Gastrointestinal disorders: Mucositis, gingivitis, stomatitis, glossitis, decreased appetite (anorexia), nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melaena, gastrointestinal ulceration and bleeding, pancreatitis, intestinal perforation, non-infectious peritonitis, toxic megacolon, malabsorption, enteritis.

Hepatobiliary disorders: Hepatic failure, acute and chronic hepatotoxicity, acute liver atrophy, necrosis, fatty metamorphosis, chronic fibrosis, acute hepatitis, periportal fibrosis, hepatic cirrhosis, liver enzyme elevations, increased transaminases, blood lactate dehydrogenase increased, decreased serum albumin. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month after cessation of therapy.

Renal and urinary disorders: Renal failure, severe nephropathy, dysuria, azotaemia, cystitis, haematuria, proteinuria, urogenital dysfunction.

Pregnancy, puerperium and perinatal conditions: Abortion, fetal defects, fetal death.

Reproductive system disorders: Defective oogenesis/spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, vaginal bleeding, vaginal ulceration, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence.

Cardiac disorders: Pericarditis, pericardial effusion, pericardial tamponade, pulmonary oedema.

Vascular disorders: Vasculitis, hypotension, thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolism).

Nervous system disorders: Paraesthesia, headaches, dizziness, drowsiness, convulsions, aphasia, hemiparesis, speech impairment, paresis, dysarthria, lethargy, motor dysfunction, cranial nerve disorder, cranial nerve palsies, leucoencephalopathy, encephalopathy, CSF pressure increased, neurotoxicity, arachnoiditis, coma, paraplegia, stupor, ataxia, dementia, unusual cranial sensations, Guillain-Barre syndrome, brain oedema.

Psychiatric disorders: Depression, confusional state, irritability, transient cognitive dysfunction, mood altered.

Respiratory, thoracic and mediastinal disorders: Pneumonitis, interstitial pneumonitis (including fatalities), respiratory failure, respiratory fibrosis, interstitial pulmonary fibrosis, reversible eosinophilic pulmonary infiltrates, chronic interstitial pulmonary disease, pharyngitis, alveolitis, pleural effusion, pleurisy, dyspnoea, chest pain, hypoxia, cough (especially dry and non-productive). Pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications.

Eye disorders: Conjunctivitis, blurred vision, eye discomfort, serious visual changes, transient blindness/vision loss.

Ear and labyrinth disorders: Tinnitus.

Infections and infestations: Infections (including fatal sepsis), decreased resistance to infection, opportunistic infections (sometimes fatal in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases), *Pneumocystis jirovecii* pneumonia (most common infection), respiratory tract infection, cutaneous bacterial infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex hepatitis, disseminated herpes simplex, cytomegalovirus infection (including cytomegaloviral pneumonia), reactivation of hepatitis B infection, worsening of hepatitis C infection.

Neoplasms benign, malignant, and unspecified (including cysts and polyps): Lymphoma (including reversible lymphoma), tumour lysis syndrome, melanoma and non-melanoma skin cancer.

Metabolism and nutrition disorders: Diabetes mellitus, metabolic disorder.

Musculoskeletal, connective tissue and bone disorders: Osteoporosis, osteonecrosis (aseptic necrosis of the femoral head), soft tissue necrosis, abnormal tissue cell changes, arthralgia/myalgia, stress fracture, back pain, nuchal rigidity.

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It

allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Signs and symptoms

In post-marketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose has also been reported.

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

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have also been cases of fatal intrathecal overdose, in which cerebellar herniation associated with increased intracranial pressure and acute toxic encephalopathy were reported.

Treatment

Folinic acid (calcium folinate) neutralises effectively the immediate toxic effects of methotrexate. After an inadvertent overdosage of methotrexate, calcium folinate should be given as soon as possible and preferably started within 1 hour after the administration of methotrexate. As the time interval between methotrexate administration and folinic acid initiation increases, the effectiveness of folinic acid in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with folinic acid.

Calcium folinate should be given at 10 mg/m² IV or IM every 6 hours until the serum methotrexate levels are below 10⁻⁸ M. In the presence of gastric stasis or obstruction calcium folinate should be administered parenterally. Concomitant hydration (3 L/d) and urinary alkalinisation with sodium bicarbonate should be employed. The bicarbonate dose should be adjusted to maintain a urinary pH at 7 or greater. Serum samples should be assayed for creatinine levels and methotrexate levels at 24 hour intervals. If the 24 hour serum creatinine level has increased 50% over baseline or if the 24 hour methotrexate level is >5 x 10⁻⁶ M or the 48 hour methotrexate level is 9 x 10⁻⁷ M or higher, the doses of calcium folinate should be increased to 100 mg/m² IV every 3 hours until the methotrexate level is <10⁻⁸ M. The infusion rate of calcium folinate should not exceed 16.0 mL (160 mg calcium folinate) per minute. Patients with significant third space accumulations should be considered high-risk and closely monitored until serum methotrexate levels are <10⁻⁸ M regardless of their 24 hour serum concentration.

The above mentioned statements on calcium folinate dosage do not apply with high-dosage

methotrexate therapy. The dosages of calcium folinate have varied in different studies and the published literature on high-dosage methotrexate should be consulted.

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

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic (intravenous) folinic acid, alkaline diuresis, and rapid CSF drainage and ventriculolumbar perfusion.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action

Methotrexate has as its principal mechanism of action the competitive inhibition of the enzyme folic acid reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme in the process of DNA synthesis and cellular replication. Methotrexate inhibits the reduction of folic acid and interferes with tissue cell reproduction. Methotrexate is a phase specific substance. Its main effect is directed to the S-phase of cell division. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to the effects of methotrexate. Cellular proliferation in malignant tissue is greater than in most normal tissue and thus methotrexate may impair malignant growth without irreversible damage to normal tissues.

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

Clinical Trials

No data available.

5.2 Pharmacokinetics properties

Absorption

After parenteral injection, peak serum levels are seen in about 0.25 – 2.0 hours.

Distribution

Approximately one half of absorbed methotrexate is reversibly bound to serum protein, but exchanges with body fluids easily and diffuses into the body tissue cells.

Methotrexate does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when

given orally or parenterally. High concentrations of the drug when needed may be attained by direct intrathecal administration.

Metabolism

Methotrexate does not appear to be appreciably metabolised. It is predominantly excreted by the kidneys and small amounts appear in the faeces. Approximately 10% of the administered methotrexate dose is metabolised intra-hepatically. The principal metabolite is 7-hydroxymethotrexate.

Excretion

Elimination is triphasic. The first phase probably describes distribution into organs; the second, renal excretion; and the third, passing of methotrexate into the enterohepatic circulation. Excretion occurs mainly through the kidneys. Approximately 41% of the dose is excreted unchanged in the urine during the first six hours; 90% within 24 hours. Repeated daily doses result in more sustained serum levels and some retention of methotrexate over each 24 hour period which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions.

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/10T_{1/2} clone 8 cells and was associated with an increased incidence of large colony mutants at the tk locus in L5178Y/tk[±] 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.

6. Pharmaceutical Particulars

6.1 List of excipients

Water for injection, sodium hydroxide

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 expiry date.

6.4 Special precautions for storage

DBL® Methotrexate Injection BP should be stored below 25°C and protected from light.

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.

6.5 Special precautions for disposal

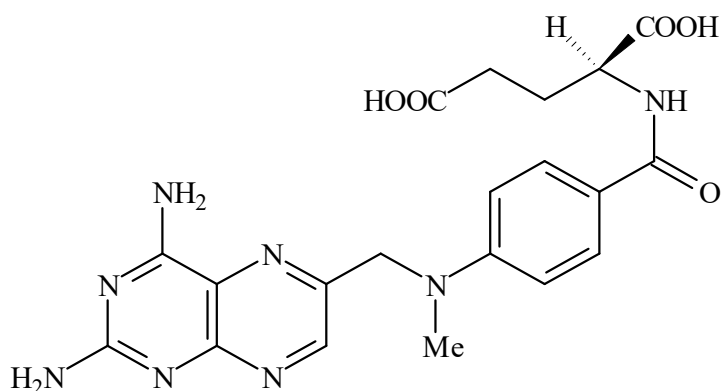
Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel or adsorbent granules. Collect up the towel of absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

6.6 Physicochemical properties

Methotrexate is a yellow-orange, crystalline powder, practically insoluble in water, alcohol, ether and ethylene chloride. It dissolves in dilute solutions of mineral acids and dilute solutions of alkali hydroxides and carbonates.

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 the Manufacturer

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

Date of Revision: 22 OCT 2024

DBL® METHOTREXATE-1024