AUSTRALIAN PRODUCT INFORMATION - METHOBLASTIN® (METHOREXATE) TABLETS

WARNINGS

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

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved and should be under his constant supervision.

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, but only when the diagnosis has been established by biopsy and/or after appropriate consultation.

Potential of fatal toxicity from dosing errors

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 (see Section 4.2 and 4.4, 4.9). For the same reason great care should be taken with dispensing to ensure the correct tablet strength of Methoblastin is given to the patient. Methoblastin is available as 2.5 mg and 10 mg tablets.

Organ system toxicity

Gastrointestinal

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

Gastrointestinal toxicity has been reported with concomitant administration of methotrexate (usually in high doses) along with nonsteroidal anti-inflammatory agents (NSAIDs).

Haematological

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

Unexpectedly severe (sometimes fatal) marrow suppression and aplastic anaemia have been reported with concomitant administration of methotrexate (usually in high doses) along with NSAIDs.

Hepatic

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.

Musculoskeletal

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

Infection or Immunologic States Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy.

Immunisation

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

Pulmonary

Methotrexate-induced lung disease including acute or chronic interstitial pneumonitis 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.

Renal

Impaired renal function is usually a contraindication.

Malignant lymphomas

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.

Fetal toxicity

Use in Pregnancy

Pregnancy category D

Methotrexate has caused fetal death and/or congenital abnormalities. Therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic and rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

1. PRODUCT NAME

Methotrexate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Methoblastin 2.5 mg tablet contains 2.5 mg of methotrexate.

Each Methoblastin 10 mg tablet contains 10 mg of methotrexate.

Excipient(s) with known effect

Methoblastin 2.5 mg tablets and 10 mg tablets contain 42 mg and 38.5 mg of lactose monohydrate, respectively.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablets.

Methoblastin 2.5 mg tablets are yellow, round, biconvex, engraved M 2.5 on one side and blank on the other.

Methoblastin 10 mg tablets are yellow, capsule shaped, engraved M 10 on the same side as the score line.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Antineoplastic Chemotherapy

Treatment of breast cancer, gestational choriocarcinoma and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic leukaemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukaemias. In combination with corticosteroids, methotrexate may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. Methoblastin is also effective in the treatment of the advanced stages (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

Psoriasis Chemotherapy

(See WARNINGS box and Section 4.4)

Because of the high risk attending to its use, Methoblastin is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and / or after dermatologic consultations.

Rheumatoid Arthritis Chemotherapy

(See WARNINGS box and Section 4.4)

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 (see Section 4.4, and 4.5).

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

Dose

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.

Prescribers should advise the patient of the dosing regimen for their awareness and obtain at least a verbal indication from the patient that they have understood the dosing regimen.

Pharmacists should clearly indicate the dosing regimen on the dispensing label at the point of dispensing and obtain at least a verbal indication from the patient that they have understood the dosing regimen.

Antineoplastic Chemotherapy

Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

For conversion of mg/kg bodyweight to mg/m^2 of body surface area or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Breast Carcinoma

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

Choriocarcinoma and similar trophoblastic diseases

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

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

One to two courses of methotrexate after normalisation of βHCG is usually recommended. Before each course of the drug, careful clinical assessment is essential.

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

Leukaemia

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 alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. More recently, corticosteroid therapy in combination with other antileukaemic drugs or in cyclic combination therapy including methotrexate, has produced rapid and effective remissions.

Methotrexate alone, or in combination with other agents, appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, by administering methotrexate 2 times weekly in doses of 30 mg/m^2. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

Lymphomas

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

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

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

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

Hodgkin's Disease responds poorly to methotrexate and to most types of chemotherapy.

Mycosis Fungoides

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

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

Weekly Dosage Regimens

Psoriasis Chemotherapy

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

There are three commonly used general types of dosage schedules:

(1) weekly oral 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. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy.

Recommended Starting Dose Schedules

1. Weekly single oral dose schedules: 10 – 25 mg per week until adequate response is achieved. The maximum dose of 50 mg per week should not be exceeded.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses or at 8 hour intervals for four doses, each week. The maximum dose of 30 mg per week should not be exceeded.

3. Daily oral dose schedule: 2.5 mg daily for five days followed by at least a two day rest period. The maximum dose of 6.25 mg per day should not be exceeded.

Dosage in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule. Once optimal clinical response has been achieved each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as full blood count, 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 during and for at least twelve weeks following methotrexate therapy.

Rheumatoid Arthritis Chemotherapy

The two commonly used weekly dosage schedule are:

1. Starting dosage is a single oral dose of 7.5 mg once weekly

2. A divided oral doses of 2.5 mg at 12 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 12 weeks or more.

In non-responsive patients, the dosage in each schedule may be increased to 15 mg/week after six weeks. If necessary, dosage may be gradually increased further to achieve optimal response, to a maximum total weekly dose 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 possible 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.

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

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

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see WARNINGS box, Section 4.4 and 4.9).

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.

Dose Adjustments

Renal Impairment

Methotrexate is excreted primarily by the kidneys. In patients with renal impairment the dose may need to be adjusted to prevent accumulation of drug (see Section 4.4, Organ System Toxicity, Renal).

Special populations

Elderly

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasised to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis (see Section 4.4, Use with caution in the following circumstances).

Paediatric population

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

Method of Administration

Oral administration

4.3 CONTRAINDICATIONS

Methotrexate should not be given to:

Pregnant women (see Section 4.6, Use in Pregnancy).

Breast-feeding women (see Section 4.6, Use in Lactation).

Patients with severe hepatic impairment.

Patients with severe renal impairment.

Patients with alcoholism or alcoholic liver disease.

Patients who have overt or laboratory evidence of immunodeficiency syndromes.

Patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.

Patients with severe, acute or chronic infections.

Patients with a known hypersensitivity to methotrexate or to any of the excipients.

Psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis.

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

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

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.

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

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

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, but only when the diagnosis has been established, as by biopsy and/or after appropriate consultation.

Methotrexate should be used with extreme caution in the presence of debility and in extreme youth or age (see Section 4.2 Elderly (> 65 years old) and Section 4.2 Paediatric population).

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.

Folinic acid deficiency

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

Adequate folinic acid (calcium folinate) protection is indicated in high-dose methotrexate therapy. The administration of calcium folinate, hydration, and urine alkalisation 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).

Folinic acid deficiency states may increase methotrexate toxicity.

Hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs)

Concomitant use of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs, e.g. leflunomide) is not advisable (see Section 4.5).

Organ System Toxicity

Gastrointestinal

Methotrexate should be used with extreme caution in the presence/history of infection, peptic ulcer and ulcerative colitis. Use in patients with active gastrointestinal ulcer disease is contraindicated.

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

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

Haematologic

Methotrexate may produce marked depression of bone marrow, anaemia, leukopenia, 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).

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

Pretreatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression, manifesting as anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate discontinuation and institution of appropriate therapy.

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

In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression.

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, Antibiotics, Oral Antibiotics).

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

Hepatic

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

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 do not appear predictive of subsequent hepatic disease.

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, Liver Function Tests in this section). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

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

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

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.

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.

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

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). There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy.

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.

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 x-ray. This lesion can occur at all dosages. 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.

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

Patients should be monitored for pulmonary signs and symptoms at each follow-up visit.

Neurotoxicity

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

Renal

Due to delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate (see Section 4.2 and4.3).

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. Caution should be exercised if renal impairment is disclosed.

Drug dosage should be reduced or discontinued until renal function is improved or restored. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7. A high fluid throughput and alkalinisation of the urine 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). Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least first 24 hours after the administration of methotrexate is started.

Significant renal insufficiency is contraindicated for methotrexate therapy (see Section 4.3).

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

Skin

Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis, 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 Test Monitoring of Patients

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 and liver function tests. A chest X-ray is also recommended. The tests should be performed prior to therapy, at appropriate periods during therapy, and after termination of therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration), more frequent monitoring may also be indicated.

During therapy for rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: haematology at least monthly, and liver 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 Organ system toxicity, Pulmonary in this section).

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).

Liver Function Tests/Liver Biopsy

Treatment should not be instituted or should be discontinued if any abnormalities of liver function tests, or liver biopsy, are present or develop during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients. In the case of a constant increase in liver-related enzyme, a reduction of the dose or discontinuation of therapy should be taken into consideration. Closer monitoring of liver enzymes is necessary especially in patients taking other hepatotoxic or haematotoxic medicinal products (e.g., leflunomide).

More frequent check-ups of liver function may become necessary during the initial phase of treatment, when the dose is increased and during episodes of a higher risk of elevated methotrexate blood levels (e.g. dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as NSAIDs).

Repeated liver biopsies are recommended after a cumulative dose of 1.0 g – 1.5 g is achieved. Liver biopsies are also recommended for patients with elevated risk factors for hepatotoxicity. Liver biopsy is also not necessary in the following cases: elderly patients, patients with an acute disease, patients with contraindication for liver biopsy (e.g. cardiac instability, altered blood coagulation parameters) or patients with poor expectance of life.

Liver biopsy is recommended for patients during or shortly after initiation of therapy with methotrexate. Since a small percentage of patients discontinue therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase. It should be performed when longer therapy can be assumed.

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. The need for liver biopsy should be evaluated on an individual basis. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment.

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.

Rheumatoid arthritis

Age at first use of methotrexate and duration of therapy have 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 to 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 biopsy, or in any patient whose liver biopsy shows mild to severe changes (Roenigk grade IIIb or IV). When methotrexate is discontinued, a 'flare' of arthritis usually occurs within three to six weeks.

Information for Patients

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

Patients should be informed that the dose of methotrexate is once weekly in the treatment of rheumatoid arthritis and psoriasis (see Section 4.2). The prescriber should specify the day of intake on the prescription. Pharmacists should clearly indicate the day of the week the weekly dose is to be taken on the dispensing label. Patients should be aware of the importance of adhering to the once weekly intake and that daily administration can lead to serious toxic effects.

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

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

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

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

Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.

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

Methoblastin tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION 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).

Asparaginase

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

Mercaptopurine

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

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, sulphonamides, sulphonylureas, phenylbutazone, phenytoin, and some antibacterials such as penicillins, tetracycline, chloramphenicol, pristinamycin, probenecid and para-aminobenzoic acid. When methotrexate is used concurrently with these drugs, its toxicity may be increased.

Hypolipidaemic Compounds

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

Probenecid and Drugs Reducing Tubular Secretion

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

DMARDs and 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 and gastrointestinal toxicity**.**

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

Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with some 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.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have included concurrent use of dosage regimens of NSAIDs without apparent problems. However, doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis. 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.

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

Antibiotics

Ciprofloxacin

Renal tubular transport is diminished by ciprofloxacin s; 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.

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

Agents that may affect bone marrow

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.

Vitamins

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

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).

Leflunomide

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

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. This effect can be reduced by the use of folinic acid rescue (see Section 4.9).

Amiodarone

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

Psoralen plus Ultraviolet Light (PUVA) Therapy

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

Packed Red Blood Cells

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

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 (see Section 4.3).

Theophylline

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

Diuretics

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

Proton Pump Inhibitors

Coadministration of proton pump inhibitors (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.

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.

Cyclosporin and other Immune-Modulating Agents

Cyclosporin 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 six 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.

The possible risks of effects on reproduction should be discussed with patients of childbearing potential (see Use in Pregnancy section below).

Use in Pregnancy

Pregnancy Category D.

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

Methotrexate has been shown to be teratogenic. It has caused fetal death and/or congenital abnormalities in humans; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks.

Women of childbearing potential should not be started on methotrexate until any existing pregnancy is excluded with certainty, e.g., pregnancy test prior to initiating therapy.

Both male and female patients should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided and reliable effective contraception used if either partner is receiving methotrexate, during and for a minimum of six months (see Warnings box and Section 4.3) after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

Use in Lactation

Methotrexate passes into breast milk and is contraindicated during breastfeeding (see Section 4.3). 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 MACHINERY

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 Section 4.4 and 4.9).

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

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

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

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

Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps): Lymphoma (including reversible lymphoma), tumour lysis syndrome.

Blood and Lymphatic System Disorders: Bone marrow depression, leukopenia, neutropenia, thrombocytopenia, anaemia, aplastic anaemia, megaloblastic anaemia, eosinophilia, pancytopenia, agranulocytosis, lymphadenopathy, lymphoproliferative disorders, haemorrhage (from various sites).

Immune System Disorders: Anaphylactoid reaction, anaphylactic reaction, hypogammaglobulinaemia.

Metabolism and Nutrition Disorders: Diabetes mellitus, metabolic disorder.

Psychiatric Disorders: Depression, confusion, irritability, transient subtle cognitive dysfunction, mood alteration.

Nervous System Disorders: Paraesthesia, headaches, dizziness, drowsiness, convulsions, aphasia, hemiparesis, speech impairment, paresis, dysarthria, lethargy, motor dysfunction, cranial nerve palsies, leukoencephalopathy, encephalopathy, CSF pressure increased, neurotoxicity, arachnoiditis, coma, paraplegia, stupor, ataxia, dementia, unusual cranial sensations.

Eye Disorders: Conjunctivitis, blurred vision, eye discomfort, serious visual changes of unknown aetiology including transient blindness.

Ear and Labyrinth Disorders: Tinnitus.

Cardiac Disorders: Pericarditis, pericardial effusion, pericardial tamponade.

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

Respiratory, Thoracic and Mediastinal Disorders: Pneumonitis, interstitial pneumonitis deaths, interstitial pulmonary fibrosis, reversible eosinophilic pulmonary infiltrates chronic interstitial obstructive pulmonary disease, pulmonary alveolar haemorrhage (has been reported for methotrexate used in rheumatologic and related indications), pharyngitis, alveolitis, pleural effusion, pleurisy, dyspnoea, chest pain, hypoxia, cough (especially dry and non-productive).

Gastrointestinal Disorders: Mucositis, gingivitis, stomatitis, glossitis, anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melaena, gastrointestinal ulceration (including oral ulcers) and bleeding, pancreatitis, intestinal perforation, noninfectious peritonitis, toxic megacolon, malabsorption, enteritis.

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

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, painful damage to psoriatic lesions, skin ulceration, skin necrosis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentation disorder (depigmentation/hyperpigmentation), alopecia, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes, nail hyperpigmentation, acute paronychia.

Musculoskeletal, Connective Tissue and Bone Disorders: Osteoporosis, osteonecrosis (aseptic necrosis of the femoral head), soft tissue necrosis, abnormal tissue cell changes, arthralgia/myalgia, stress fracture.

Renal and Urinary Disorders: Renal failure, severe nephropathy, dysuria, azotaemia, cystitis, haematuria, proteinuria, urogenital dysfunction.

Pregnancy, Puerperium and Perinatal Conditions: Abortion, fetal defects, fetal death

Reproductive System Disorders: Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility**,** vaginal bleeding, vaginal ulceration, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence.

General Disorders and Administration Site Conditions: Sudden death, increased rheumatoid nodules, pyrexia, chills, malaise, fatigue.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

Signs and Symptoms

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

Treatment of Overdosage

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

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/m^2 IV or IM q 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/m^2 IV q 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 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 the drug and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. However, effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialysator.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26(Australia).

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.

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 induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions 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 information supplied

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Orally administered methotrexate is absorbed rapidly in most, but not all, patients and reaches peak serum levels within 1 to 2 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

Methabolism

No information supplied.

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/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.

Methotrexate causes embryotoxicity, abortion and fetal defects in humans.

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.

Assessment of the carcinogenic potential of methotrexate is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. 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 PARTICUALRS

6.1 LIST OF EXCIPIENTS

Maize starch, lactose monohydrate, pregelatinised maize starch, polysorbate 80, microcrystalline cellulose and magnesium stearate.

6.2 INCOMPATIBILITIES

Methotrexate is incompatible with cytarabine, fluorouracil and prednisolone.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottle with a child-resistant closure.

Methoblastin 2.5 mg tablets are supplied in pack-sizes of 30 uncoated tablets.

Methoblastin 10 mg tablets are supplied in pack-sizes of 15 and 30 uncoated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

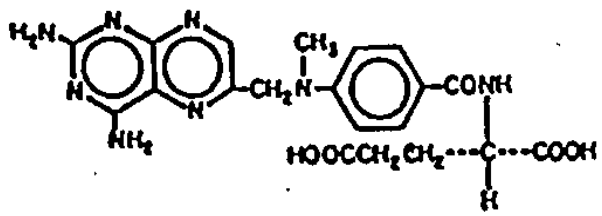
Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects.

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

Pregnant staff should be excluded from working with this drug.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structural



CAS number

59-05-2

Methotrexate is a yellow or orange crystalline powder. It is practically insoluble in water, in alcohol and in methylene hydrochloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114.

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

23 September 1991.

10. DATE OF REVISION

11 May 2018.

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.8	Pulmonary alveolar haemorrhage reported with methotrexate used in rheumatoid arthritis and related indications. Change to SPC format.