

NEW ZEALAND DATA SHEET
METHOTREXATE EBEWE INJECTION CONCENTRATE (METHOTREXATE BP)

WARNINGS

METHOTREXATE EBEWE (METHOTREXATE 100 MG/ML) IS RECOMMENDED FOR INTRAVENOUS ADMINISTRATION ONLY.

METHOTREXATE MUST BE USED ONLY BY DOCTORS EXPERIENCED IN ANTIMETABOLITE CHEMOTHERAPY OR IN THE CASE OF NON-ONCOLOGICAL CONDITIONS, BY A SPECIALIST DOCTOR.

BECAUSE OF THE POSSIBILITY OF FATAL OR SEVERE TOXIC REACTIONS, THE PATIENT-SHOULD BE FULLY INFORMED BY THE DOCTOR 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, METHOTREXATE USE SHOULD BE RESTRICTED TO SEVERE, RECALCITRANT, DISABLING DISEASE THAT IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY, AND ONLY WHEN THE DIAGNOSIS HAS BEEN ESTABLISHED, BY BIOPSY AND/OR AFTER APPROPRIATE CONSULTATION.

1. Methotrexate may produce marked depression of the bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.
2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of 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 methotrexate with other drugs with hepatotoxic potential or alcohol should be avoided.
3. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
4. Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy.
5. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.
6. Unexpectedly serious adverse effects including severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with nonsteroidal anti-inflammatory drugs (NSAIDs).

7. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
8. Pulmonary toxicity including acute or chronic interstitial pneumonitis, pleural effusion and pulmonary fibrosis, which can progress rapidly and is potentially fatal, has been associated with methotrexate therapy. It may occur acutely at any time during therapy and has been reported at low doses. Methotrexate should be discontinued and careful clinical evaluation be performed in patients developing symptoms of pulmonary toxicity (e.g. dry, non-productive cough and dyspnoea). Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded in patients presenting with symptoms of pulmonary toxicity. Management of methotrexate induced pulmonary toxicity is mainly supportive. Methotrexate induced pulmonary toxicity may not be fully reversible. Patients should be closely monitored for pulmonary symptoms.
9. Methotrexate has been used in high dosage schedules followed by calcium folinate (leucovorin calcium) in the adjuvant treatment of certain neoplastic diseases. This procedure is complicated and hazardous. It should not be attempted except by highly experienced teams following carefully designed protocols. The recent published literature should always be consulted.
10. **Impaired Renal function** Methotrexate is usually contraindicated in patients with impaired renal function.

11. **Use in pregnancy** (Category D)

Methotrexate has caused foetal death and/or congenital anomalies. It should not be used in pregnant women, or in those who might become pregnant, unless the potential benefits can be expected to outweigh the considered risks. Methotrexate is contraindicated in the treatment of psoriasis in pregnant women. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 6 months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

12. **Use in lactation**

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

13. **Use in children**

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

14. Only preservative-free methotrexate should be used for intrathecal administration.

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

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

1. PRODUCT NAME

Methotrexate Ebewe concentrate for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: Methotrexate BP

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

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

3. PHARMACEUTICAL FORM

Concentrate for injection:

500 mg/5 mL, 1000 mg/10 mL, 5000 mg/50 mL.

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 and the palliation of acute and subacute lymphocytic leukaemia (greatest effect has been observed in palliation of acute lymphoblastic (stem-cell) leukaemias). Methotrexate is now most commonly used for the maintenance of medicine induced remissions.

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 that 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 dermatological consultation.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

BECAUSE OF THE 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.

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 only the first and eighth days.

Maintenance therapy for 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 other agents, appears to be the medicine of choice for securing maintenance of medicine induced remissions.

Alternatively, 2.5 mg/kg intravenously every 14 days may be given. Should relapse does 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 antifolate 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.

The prescriber should consult the appropriate scientific literature.

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

Meningeal leukaemia

Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or remain silent and be diagnosed only by examination of the cerebrospinal fluid (CSF), which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of methotrexate from blood serum to the CSF is minimal, for adequate therapy the drug is administered intrathecally. Only preservative-free methotrexate should be used for intrathecal administration. Methotrexate Ebewe is not suitable for intrathecal administration. If intrathecal methotrexate therapy is indicated, a suitable alternative formulation should be used.

High dose therapy (see Section 4.4 Special warnings and precautions for use).

Recent published literature should be consulted for details. Dosage regimens have varied considerably in different studies depending upon the nature and severity of the disease and the previous experience of the investigator are some of the factors influencing the choice of dosage and the duration of therapy. It must be emphasised that high dosages should be used only 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.

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 reinstating methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception during and for at least three months following methotrexate therapy.

The commonly used injectable dosage schedule is by weekly parenteral intermittent large doses. The schedule should be continually tailored to the individual patient. Dose schedule cited below pertain to an average 70 kg adult. 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 starting dose. Weekly single dose schedule: 10 to 25 mg IV per week until adequate response is achieved. Weekly dosage should not exceed 50mg.

Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal clinical 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.

Method of administration

Antineoplastic chemotherapy

Methotrexate Ebewe is suitable only for IV use. It should be diluted prior to administration. It is not suitable for intrathecal administration.

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.

Caution

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

4.3. CONTRAINDICATIONS

- Severe renal impairment.
- In patients being treated for psoriasis and rheumatoid arthritis: pregnancy; poor nutritional status; bone marrow depression; hepatic disorders; pre-existing blood dyscrasias (e.g. bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia).
- Rheumatoid arthritis patients with active, infectious disease or psoriasis patients with serious infections, and in psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis. Methotrexate is contraindicated in psoriatic and rheumatoid arthritis patients suffering severe renal disorders, alcoholism or hepatic disorders including alcoholic liver disease or other chronic liver disease.

- Overt or laboratory evidence of immunodeficiency syndrome(s).
- Breastfeeding.
- Known hypersensitivity to methotrexate or any of the excipients.
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.
- Radiotherapy to the central nervous system should not be given concurrently with intrathecal methotrexate.
- An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate and acitretin is also contraindicated.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Methotrexate Ebewe (methotrexate 100 mg/mL) is recommended for intravenous administration only.

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

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

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

When considering the use 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 necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyser. Caution should be exercised when reinstating methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

Methotrexate exits slowly from the third space compartments (e.g. pleural effusions or ascites). This results in a prolonged terminal phase half-life and unexpected toxicity. In patients with significant third-space accumulation, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

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

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

Like other cytotoxic medicines, methotrexate may induce tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive and pharmacological measures may prevent or alleviate this complication. Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see WARNING box and Section 4.4 Special warnings and precautions for use).

Haematologic

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

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

Gastrointestinal

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

Pulmonary

Acute or chronic interstitial pneumonitis and pleural effusion, often associated with blood eosinophilia, may occur and deaths have been reported. Rheumatoid arthritis patients are at risk to develop rheumatoid lung disease, which is often associated with interstitial pulmonary disease. Methotrexate may exacerbate this underlying lung disease

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms. The medicine should be discontinued and careful clinical evaluation should be performed in patients developing pulmonary manifestations (especially a dry, non-productive cough). Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages. (See Warning box.)

If methotrexate-induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted. Methotrexate-induced pulmonary toxicity may occur at any time during therapy and may not be fully reversible.

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

Laboratory test monitoring of patients

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

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

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

Hepatic

Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. They are usually transient and asymptomatic and do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

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

The risk of developing acute hepatitis and chronic hepatotoxicity in psoriatic patients seems to be correlated not only to the cumulative dose of the medicine 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 two years or more) and after a total cumulative dose of at least 1.5 grams.

Psoriasis

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at before start of therapy or shortly after initiation of therapy (two to four months); after a total cumulative dose of 1.5 g; and after each additional

1.0 to 1.5 g. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in six months. Milder histological findings such as fatty change and low-grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the medicine should be used with caution.

Rheumatoid arthritis

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

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

Musculoskeletal

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

Infection or immunologic states

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

Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia should be considered. The immunosuppressive action of methotrexate must be taken into consideration in evaluating the use of the medicine where immune responses in a patient may be important or essential.

Immunisation

Immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is contraindicated during therapy (see Section 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interactions).

Skin

Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's syndrome), and erythema multiforme have been reported following single

or multiple doses of methotrexate. Reactions have occurred within days of intrathecal administration. Recovery has been reported with discontinuation of therapy.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

Patients receiving immunosuppressive therapy, including methotrexate, are at an increased risk of developing skin cancer (melanoma and non-melanoma). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer and exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

When considering the use of methotrexate for chemotherapy, clinicians must evaluate the need and potential value of the medicine against the risks, adverse reactions or toxic effects. Most adverse reactions are reversible if detected early. When such reactions do occur, the dosage should be reduced or medicine discontinued and appropriate corrective measures taken. If necessary, this could include the use of leucovorin calcium and/or acute intermittent haemodialysis with a high flux dialyser. Caution should be exercised when reinstating methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

Folinic acid deficiency

Folate deficiency states may increase methotrexate toxicity. If acute methotrexate toxicity occurs, patients may require folinic acid. In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B12 levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B12 deficiency.

High dose therapy

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

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

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

sensorimotor signs, including transient blindness and abnormal reflexes. The exact cause is unknown.

Neurologic

There have been reports of leucoencephalopathy following intravenous administration of methotrexate in high doses to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalised or focal seizures, has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate dose intravenous methotrexate (1 g/m²). Symptomatic patients were commonly noted to have leucoencephalopathy, encephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

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

Discontinuation of methotrexate does not always result in complete recovery.

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

1. acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity and fever;
2. sub-acute myelopathy usually transient, characterised by e.g. paraparesis/ paraplegia and increased CSF pressure associated with involvement with one or more spinal nerve roots;
3. a delayed syndrome occurring months to years after treatment characterised by necrotising leucoencephalopathy and manifested by confusion, irritability, somnolence, ataxia, dementia, occasionally convulsions and, rarely, death. The effects are dose-related and occur particularly when intrathecal methotrexate is given at doses greater than 50 mg in combination with cranial irradiation and systemic methotrexate therapy.

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

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

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

Use in renal impairment (See Warnings box)

As methotrexate is excreted primarily by the kidney, its use in the presence of impaired renal function may lead to medicine accumulation with resultant toxicity or even additional renal damage. The renal status of the patient should be determined prior to and during methotrexate therapy. Caution should be exercised if significant renal impairment is present. Drug dosage should be reduced or discontinued until renal function is improved or restored. The urine should be kept alkaline throughout therapy with methotrexate (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0).

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

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

Use in hepatic impairment

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

Methotrexate level

Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g., pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function.

Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate folinic acid rescue is delayed for more than 42 to 48 hours.

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

Use in the elderly

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

Paediatric use

Aside from its established use in cancer chemotherapy and polyarticular-course juvenile rheumatoid arthritis, the safety and efficacy of using methotrexate in children has not been fully elucidated.

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

Effects on laboratory tests

No data available.

Instructions to patients

1. Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.
2. Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity. Baseline assessment should include a complete blood count with differential and platelet counts; hepatic enzymes; or hepatitis B or C infection testing, renal function tests; and a chest X-ray.
3. Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions and increased risk of skin cancer (non-melanoma and melanoma).

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Antibiotics

Ciprofloxacin

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

Oral antibiotics

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

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or additive antifolate effect.

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

Penicillins and sulfonamides

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

Hypolipidaemic compounds

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

Vitamins

In inflammatory arthritis, such as rheumatoid arthritis, concomitant treatment with folic acid or folic acid may decrease the incidence or severity of adverse effects from methotrexate therapy. It is not known whether these medications may decrease the efficacy of methotrexate in treating arthritis. Because vitamin preparations containing folic acid or folic acid may decrease the effectiveness or alter the responses to methotrexate these should not be given to patients taking methotrexate for conditions other than arthritis, including in the treatment of neoplastic disease.

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

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

Oncology indications: Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with high doses of methotrexate such as used in the treatment of osteosarcoma. NSAIDs elevate and prolong serum methotrexate levels, resulting in death from severe haematologic (including bone marrow suppression and aplastic anaemia) and gastrointestinal toxicity. These unexpectedly severe toxicities have been reported with concomitant administration of methotrexate and aspirin, other salicylates, asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

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

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

Probenecid

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

Allopurinol

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

Chemotherapeutic agents

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

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

Cytarabine

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

Mercaptopurine

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

L-asparaginase

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

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 Overdose), avoid concomitant use of nitrous oxide in patients receiving methotrexate. Use caution when administering methotrexate after a recent history of nitrous oxide administration.

Leflunomide

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

Amiodarone

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

Hepatotoxic agents

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

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential

hepatotoxins (e.g. leflunomide, azathioprine, retinoids, sulfasalazine and alcohol) should be closely monitored for possible increased risk of hepatotoxicity.

Theophylline

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

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 a 24-hour methotrexate infusion and subsequent transfusions have shown enhanced toxicity probably resulting from prolonged serum methotrexate concentrations.

Vaccines

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

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

Proton pump inhibitors

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

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities.

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

Diuretics

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

Phenytoin

Cytotoxic agents may impair absorption of phenytoin, which may decrease efficacy of phenytoin and increase the risk for exacerbation of convulsions. Risk of toxicity enhancement or 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.

Sodium Valproate

Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility

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

Men treated with methotrexate should use contraception and not father a child during and for six months after treatment. Methotrexate may be genotoxic and has caused increased number of abnormal and immobile spermatozoa in clinical trials. 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. The risk of genetic abnormalities may persist after discontinuing methotrexate therapy.

Pregnancy – Australian Pregnancy Category D

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 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 any existing pregnancy is excluded with certainty, e.g., by pregnancy test prior to initiating therapy.

Both male and female patients should be fully counselled on the serious risk to the fetus if pregnancy occurs while undergoing treatment.

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. UNDESIRABLE EFFECTS

Very common: greater than or equal to 1/10; common: greater than or equal to 1/100 and < 1/10; uncommon: greater than or equal to 1/1,000 and < 1/100; rare: greater than or equal to 1/10,000 and < 1/1,000 and very rare: < 1/10,000.

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

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

Skin and subcutaneous tissue disorders. Dermatitis, erythematous rashes, erythema multiforme, pruritus, urticaria, photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes, nail hyperpigmentation, acute paronychia, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Burning and erythema may appear in psoriatic areas for one to two days following each dose. Rarely, painful plaque erosions may appear. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, soft tissue necrosis and osteonecrosis have also been reported. Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis and erythema multiforme have been reported in children and adults within days of oral, intramuscular, intravenous or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Blood and lymphatic system. Bone marrow depression, leucopenia, neutropenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenia, anaemia (including aplastic anaemia), hypogammaglobulinaemia, decrease in serum albumin. Clinical sequelae such as fever, infections, haemorrhage from various sites, septicaemia, lymphadenopathy and lymphoproliferative disorders (including reversible) may be expected. Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Cardiovascular disorders. Pericarditis, vasculitis, pericardial effusion, pericardial tamponade, hypotension and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolus) have been reported with methotrexate therapy.

Alimentary system. Mucositis (gingivitis, pharyngitis, stomatitis, glossitis), decreased appetite, anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melena, gastrointestinal ulceration and bleeding, intestinal perforation, noninfectious peritonitis, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy,

necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, chronic fibrosis, or hepatic cirrhosis', elevated liver enzymes, decreased serum albumin and hepatic failure. In rare cases, the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month of cessation of therapy.

Body as a whole: soft tissue necrosis, anaphylactoid reactions.

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

Pulmonary system. Interstitial pneumonitis (including fatalities), pleural effusion, pleurisy, interstitial fibrosis, and respiratory failure, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, chronic interstitial obstructive pulmonary disease, alveolitis, death. Manifestations of methotrexate induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxia, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar). Pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications.

Nervous system. Paresthesia, encephalopathy/leucoencephalopathy, headaches, dizziness, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, cranial nerve disorder/ palsies and coma. Aphasia, hemiparesis and convulsions have occurred, possibly related to haemorrhage or to complications from intra-arterial catheterisation. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressures have followed intrathecal administration. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation. Other side effects include: neurotoxicity; arachnoiditis; paraplegia; stupor; ataxia; dementia, motor dysfunction, depression, confusional state and irritability.

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

Ear and labyrinth disorders. Tinnitus

Infections and infestations. There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. **Pneumonia (in some cases leading to respiratory failure) may occur.** *Pneumocystis jirovecii* pneumonia was the most common infection. Other reported infections include sepsis, nocardiosis, histoplasmosis, cryptococcosis, *herpes zoster*, *herpes simplex*, hepatitis and disseminated *herpes simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia, reactivation of hepatitis B infection, worsening hepatitis C infection, respiratory tract infection, cutaneous bacterial infections.

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

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

Other. Other reactions related or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporosis, osteonecrosis (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, back pain, nuchal rigidity, nodulosis, pyrexia, chills, malaise, fatigue stress fractures, loss of libido, impotence, hypogammaglobulinemia and even sudden death, have been reported.

A few cases of anaphylactoid reactions have been reported.

Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps). Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome, melanoma and non-melanoma skin cancer have been documented in patients treated with methotrexate.

Reporting suspected adverse effects

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

4.9. OVERDOSE

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

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

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

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

As soon as possible after an inadvertent overdosage of methotrexate, calcium folinate (leucovorin calcium) 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, leucovorin should be administered parenterally. Concomitant hydration (3 L/day) and urinary

alkalinisation with sodium bicarbonate should be employed. The bicarbonate dose should be adjusted to maintain a urinary pH at 7 or greater. The use of acute, intermittent haemodialysis with a high-flux dialyzer should also be considered. 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 $> 5 \times 10^{-6}$ M or the 48 hour methotrexate level is 9×10^{-7} M or higher, the doses of calcium folinate should be increased to 100 mg/m² IV every three 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.

Concomitant hydration and alkalinisation of the urine with sodium bicarbonate is recommended to prevent precipitation of methotrexate or its metabolite in the renal tubules. Patients undergoing methotrexate therapy should be advised to increase fluid intake. Neither haemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyzer.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

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

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

After parenteral injection, peak serum levels are seen in about 0.5 to 2.0 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 medicine within the tissues.

The liver cells appear to retain certain amounts of the medicine 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.

Distribution

Approximately one-half the 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 parenterally. High concentrations of the medicine when needed may be attained by direct intrathecal administration. However, Methotrexate Ebewe is not suitable for intrathecal administration.

Metabolism

No data available.

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.

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/10T1/1 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 in polychromatic erythrocytes in mice and in human bone marrow cells, a transient and reversible increase in chromosomal aberrations. 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 medicines, especially in children or young adults.

Reproductive and developmental toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium hydroxide EP, water for injections EP, nitrogen EP

6.2. INCOMPATIBILITIES

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

For information on interactions with other medicines and other forms of interactions, refer to Section 4.5 Interactions with other medicines and other forms of interactions.

6.3. SHELF LIFE

24 months from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Protect from light.

6.5. NATURE AND CONTENTS OF CONTAINER

Glass vial, 500 mg/5 mL: 1

Glass vial, 1000 mg/10 mL: 1

Glass vial, 5000 mg/50 mL: 1 (Oncology Pharmacy Bulk product)

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Handling precautions. As with all antineoplastic agents, trained personnel should prepare Methotrexate Ebewe. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). The work surface should be protected by disposable plastic backed, absorbent paper. 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 or sodium bicarbonate solution: Medical attention should be sought. It is recommended that pregnant personnel not handle cytotoxic agents such as methotrexate.

Luer-Lok 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

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. Cleanse the remaining spill area with copious amounts of water.

Methotrexate Ebewe, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1,100°C.

Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1,100°C'. Waste material should be incinerated at 1,100°C for at least one second.

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Ltd
PO Box 99102
Newmarket
Auckland 1149
Telephone 0800 354 335

9. DATE OF FIRST APPROVAL

09 December 2014

10. DATE OF REVISION OF THE TEXT

03 February 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes
4.3	Additional information included on contraindications related to rheumatoid arthritis patients
4.4	Additional information included under the following subheadings: laboratory test monitoring for patients, hepatic, rheumatoid arthritis, skin, folic acid deficiency
4.5	Additional information included under vitamins and addition of sodium valproate as per Medsafe recommendation
4.6	Update pregnancy information with the use of effective contraception.