PACKAGE INSERT

METHOTREXATE REMEDICA

PRODUCT NAME

Methotrexate Remedica 2.5 mg film-coated tablets

NAME AND STRENGTH OF ACTIVE SUBSTANCE

Each tablet contains methotrexate 2.5 mg.

PRODUCT DESCRIPTION

Film-coated tablet.

Yellow, round, film-coated tablets with Remedica's logo on one side.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, ATC code: L04AX03

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

Tissues with high rates of cellular proliferation, e.g. malignant cells, bone marrow, 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 proliferation 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 reduces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosion and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

Pharmacokinetic properties

Methotrexate at low doses (<25 mg/m^2) is well absorbed from the gastrointestinal tract; at larger doses absorption may become erratic and incomplete. Peak serum levels may be achieved within 1 to 4 hours following oral administration, and within 0.5 to 2 hours following intravenous (IV) or intramuscular (IM) administration.

Approximately 50% of the absorbed methotrexate is reversibly bound to serum protein. Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, liver and gastrointestinal tract. It also distributes into third space accumulation of fluid, e.g. ascites or pleural effusions. Methotrexate does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) when given orally or parenterally. High concentrations of the drug, when needed, may be attained by intrathecal injection.

Methotrexate does not appear to be appreciably metabolised.

Methotrexate is predominantly excreted by the kidneys and small amounts appear in the faeces. Excretion of methotrexate is reduced in the presence of impaired renal function.

CLINICAL PARTICULARS

Indications

Antineoplastic chemotherapy
Methotrexate has a broad spectrum of antineoplastic activity. It is indicated for the treatment of breast cancer, gestational choriocarcinoma, and in patients with chorioadenoma destruens and hydatidiform mole.

Methotrexate may be used in combination with other chemotherapeutic agents for the palliative treatment of acute leukaemias, particularly acute lymphoblastic leukaemia. It may also be used in the treatment of Burkitt's lymphoma, advanced stages (III and IV, Peters Staging System) of lymphosarcoma, especially in children, and in advanced cases of mycosis fungoides.

High dose therapy
In high-dose schedules, methotrexate may be effective alone or in combination therapy, in the treatment of epidermoid cancers of the head and neck, osteogenic sarcoma and bronchogenic carcinoma.

Calcium folinate (leucovorin calcium) must be used in conjunction with high dose methotrexate therapy.

Psoriasis chemotherapy
Methotrexate may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after

the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.

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

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

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

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects.

Rest and physiotherapy as indicated should be continued.

Dosage and method of administration

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens.

Weekly dosage prescriptions should specify a particular day of the week.

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

A guideline of a ratio of 1:30 is given for the con-version of mg/kg body weight to mg/m^2 body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Trophoblastic diseases: The usual dosage is 15 to 30 mg daily for a 5-day course. A repeat course may be given after a period of one or more weeks provided all signs of toxicity have disappeared. Three to five courses of therapy are usually employed. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin hormone (CGH), which should return to normal or less than 50 IU/24 h, usually after the 3rd or 4th course. Complete resolution of measurable lesion usually occurs 4 to 6 weeks later. One to two courses of methotrexate after normalization of CGH is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor 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 trophoblastic neoplasms.

Leukemia: Acute lymphatic (lymphoblastic) leukemia 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 leukemia, the prognosis for adequate response is less encouraging.

Methotrexate in doses of 3.3 mg/m^2 orally in combination with prednisolone 60 mg/m^2 daily has been given for induction of remission of lymphoblastic leukemias.

When remission and general clinical improvement have been attained, a maintenance dosage of methotrexate 30 mg/m^2 orally twice weekly may be given. This treatment is expected to produce remission in 50% of patients treated, usually within 4 to 6 weeks.

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

Lymphomas: The usual dosage of methotrexate for the treatment of stage I or II of Burkitt's lymphoma, is 10 to 25 mg per day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antineoplastic agents. In all stages courses of drug therapy are usually administered interposed with 7 to 10 days rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily.

Methotrexate is of no value in the treatment of Hodgkin’s Disease.

Mycosis fungoides: Dosage of methotrexate for the treatment of mycosis fungoides is usually 2.5 to 10 mg orally each day for weeks or months. Initial dosage and dosage adjustment are determined by patient response and hematologic monitoring.

High-dosage therapy: Recent published literature should be consulted for details; dosage regimens have varied considerably in different studies depending upon the nature and severity of the disease, the experience of the investigator etc. It must be emphasised that high dosages should be only used by qualified specialists and in hospitals where the necessary facilities are available.

In order to prevent precipitation of methotrexate in the renal tubules, the patients should maintain an adequate urine flow by drinking plenty of fluids for 2 days after a high dose injection (greater than 200 mg) and keep the urine alkaline by using sodium bicarbonate continuously for at least 24 hours afterwards.

Psoriasis chemotherapy

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

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

There are three commonly used general types of dosing schedules:
- weekly oral intermittent large doses;
- divided dose intermittent oral schedule over a 36-hour period;
- daily oral with a rest period.

All schedules should be continually tailored to the individual patient. A single test dose of 5 to 10 mg parenterally one week prior to initiation of therapy is recommended to detect any idiosyncratic reaction.

Recommended dose schedules for a 70kg adult are:
- Weekly single oral dose schedule: 10 to 25 mg per week until adequate response is achieved. Weekly dosage should not exceed 50 mg.
- Divided oral dose schedule: 2.5 mg orally at 12-hour intervals for three doses or at 8-hour intervals for four doses each week. Weekly dosage should not exceed 30 mg.
- Daily dose schedule: 2.5 mg orally daily for five days followed by a rest period of at least 2 days. Daily dosage should not exceed 6.25 mg.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal response is 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.

<u>Rheumatoid arthritis chemotherapy</u>
The patient should be fully informed of the risks involved and should be under constant supervision of the doctor.

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

Both the doctor and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens: mistaken daily use may cause serious and sometimes life threatening or fatal toxicity.

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

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

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

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

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

Instructions for handling
The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good handling technique.
- Pregnant staff should be excluded from working with this drug.
- A designated area should be assigned for preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper.
- All items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration accidental contact with the skin or eyes should be treated immediately by copious.
- Lavage with water or sodium bicarbonate solution; medical attention should be sought.

Contraindications

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

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

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

Warnings and precautions

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

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

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

1. Methotrexate may produce depression of the bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.
2. At high or prolonged doses, methotrexate may be hepatotoxic. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastro-intestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential and alcohol should be avoided.
3. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
4. Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy.
5. **Use in pregnancy**: 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 and rheumatoid arthritis in pregnant women. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving

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

6. Methotrexate is usually contraindicated in patients with impaired renal function.
7. Serious adverse effects including marrow suppression, aplastic anaemia, gastrointestinal toxicity and death have been reported with concomitant administration of methotrexate (usually in high doses) with non-steroidal anti-inflammatory drugs (NSAIDs).
8. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
9. Pulmonary toxicity including acute or chronic interstitial pneumonitis and pulmonary fibrosis, which can progress rapidly and is potentially fatal, has been associated with methotrexate therapy. It may occur acutely at any time during therapy and has been reported at low doses. Methotrexate should be discontinued and careful clinical evaluation be performed in patients developing symptoms of pulmonary toxicity (e.g. dry, non-productive cough, dyspnoea). Management of methotrexate-induced pulmonary toxicity is mainly supportive. Methotrexate-induced pulmonary toxicity may not be fully reversible. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.
10. Methotrexate has been used in high-dosage schedules followed by calcium folinate (leucovorin calcium) in the adjuvant treatment of certain neoplastic diseases. This procedure is complicated and hazardous. It should not be attempted except by highly experienced teams following carefully designed protocols. The recent published literature should always be consulted.
11. **Use in children**: Aside from its established use in cancer chemotherapy; the safety and efficacy of using methotrexate in children has not been fully elucidated.
12. Only preservative-free methotrexate should be used for intrathecal administration.
13. Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity. For the same reason great care should be taken with dispensing to ensure the correct tablet strength of methotrexate is given to the patient.
14. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Methotrexate has a high potential for toxicity, which is usually dose-related. The physician should be familiar with the various characteristics of the drug and its established clinical usage. Because the toxic effects can occur at any time during methotrexate therapy, patients must be kept under appropriate supervision so that signs or symptoms of possible toxicity or adverse effects may be detected as early as possible. This is especially important in patients undergoing high dose therapy or in those where drug elimination could be impaired (renal impairment, pleural effusion, ascites). When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

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

Check the following before and during use

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

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

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

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

The following laboratory tests should be carried out as part of the essential clinical evaluation and appropriate monitoring of patients on methotrexate therapy; complete haemogram; haematocrit; urinalysis; renal and liver function tests. A chest x-ray is recommended. The tests should be performed prior to, during and after therapy. During therapy for psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, liver and renal function every one to three months. More frequent monitoring is usually indicated during antineoplastic therapy. It is important to perform liver biopsy or bone marrow aspiration studies where high dose or long-term therapy is being followed.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

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

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

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

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

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

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

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

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

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at:

1) before start of therapy or shortly after initiation of therapy (2 – 4 months);
2) after a total cumulative dose of 1.5 grams; and
3) after each additional 1.0 to 1.5 grams.

In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low-grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, methotrexate should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy has been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4 – 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy, or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

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

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

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

Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal administration. Recovery has been reported with discontinuation of therapy.

When considering the use of methotrexate for chemotherapy, clinicians must evaluate the need and potential value of the drug against the risks, adverse effects or toxic effects. Most adverse effects are reversible if detected early.

When such reactions do occur, the dosage should be reduced or drug discontinued and appropriate corrective measures taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyser. Caution should be exercised when reinstituting methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

High dose therapy

Methotrexate has been used in very high dosage followed by leucovorin rescue in the experimental treatment of certain neoplastic disease. This procedure is investigational and hazardous. It should not be attempted outside of facilities where the necessary expertise and resources have been assembled. The recent published literature should be consulted. Large doses should not be used in patients with impaired renal function or a third-space reservoir such as ascites or large pleural effusion. Renal function and serum levels should be carefully monitored in order to reveal potential toxicity. Administration of calcium folinate is mandatory in high-dose methotrexate therapy. The administration of calcium folinate, hydration and alkalinisation of the urine should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate in order to prevent renal precipitation in acidic urine.

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

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

Systemic high doses or intrathecal administration of methotrexate may cause significant CNS toxicity. Patients should be closely monitored for neurologic symptoms and if these occur treatment should be discontinued and appropriate therapy instituted.

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

Carcinogenesis, Mutagenesis, impairment of fertility

Methotrexate is considered to be carcinogenic. However, extensive epidemiologic studies are required to determine its carcinogenicity potential. Methotrexate has been reported to cause chromosome damage. Methotrexate may cause defective oogenesis and spermatogenesis. Therefore, in men and women of fertile age, steps should be taken to avoid conception during methotrexate therapy. The risk of genetic abnormalities may

persist after discontinuing methotrexate therapy. Thus, it is advised that both men and women avoid intercourse leading to conception for an indefinite period (at least 12 weeks) after discontinuing methotrexate to ensure the re-establishment of normal germinal cells.

Interactions

As methotrexate is partly bound to serum proteins, its toxicity may be increased as a result of displacement by certain drugs such as salicylates, phenylbutazone, sulphonamides, sulphonylureas, phenytoin, tetracyclines, chloramphenicol and para-aminobenzoic acid. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

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

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

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

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

NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. NSAIDs elevate and prolong serum methotrexate levels, resulting in deaths from severe haematologic and gastrointestinal toxicity. These unexpectedly severe toxicities have been reported with concomitant administration of methotrexate and aspirin, other salicylates, asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

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

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid

arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and the larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

Probenecid may increase the methotrexate plasma half-life and thereby increase blood levels. A potential interaction may exist between methotrexate and proton pump inhibitors (e.g. omeprazole, pantoprazole). Concomitant use of allopurinol with methotrexate may result in an increased incidence of cytotoxic-induced bone marrow depression.

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

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

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

Assay for folate: Methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency. The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe, unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of calcium folinate.

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

An increased risk of hepatotoxicity has been reported when methotrexate and etretinate are given concurrently (see 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, and sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity. Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

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

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

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

Skin cancer has been reported in a few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving concomitant treatment with methotrexate plus PUVA therapy (methoxsalen and ultraviolet light).
Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum methotrexate concentrations.

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

Incompatibilities

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

Instructions to patients

- 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 should be informed of the early signs and symptoms of toxicity, of the need to see their doctor promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.
- Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.
- Adverse reactions to methotrexate, such as dizziness and fatigue may affect the ability to drive or operate machinery.

Pregnancy and lactation

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

partner is receiving methotrexate, during and for at least 12 weeks after cessation of therapy.

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

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.

Adverse effects

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

Ulcerative stomatitis, leukopenia, nausea, and abdominal distress are the most common adverse effects. Others reported include malaise, undue fatigue, chills and fever, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection.

The incidence and severity of side effects generally appear to be dose and frequency related. Adverse effects have been reported for the various systems:

Skin: dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes. Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Rarely, painful plaque erosions may appear. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, soft tissue necrosis and osteonecrosis have also been reported. Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme have been reported in children and adults within days of oral, intramuscular, intravenous or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate or high doses of methotrexate in patients with neoplastic and nonneoplastic diseases.

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

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

Alimentary system: mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melena, gastrointestinal ulceration and bleeding, intestinal perforation, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, or hepatic cirrhosis', elevated liver enzymes, decreased serum albumin and hepatic failure. In rare cases, the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month of cessation of therapy.

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

Pulmonary system: interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis, death. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

Central nervous system: headaches, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, and coma. Aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressures have followed intrathecal administration. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation. There have been reports of leucoencephalopathy following IV administration of methotrexate in high doses to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalised or focal seizures, has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 gram/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy, encephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

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

1) chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity and fever;
2) paresis, usually transient, manifested by paraplegia and increased CSF pressure

3) associated with involvement with one or more spinal nerve roots;
4) 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.

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

Infections: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis carinii pneumonia was the most common infection. Other reported infections include pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes Zoster, H. simplex hepatitis*, disseminated *H. simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia.

Carcinogenicity: Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome have been documented in patients treated with methotrexate. Other reactions related to or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporotic effects (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, nodulosis, stress fractures, loss of libido, impotence and even sudden death, have been reported.

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

Overdose

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

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

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. In general, when overdosage is suspected, the dose of calcium folinate should be equal to or higher than the offending dose of methotrexate, and should be given as soon as possible, preferably

within the first hour after which it is much less effective. Calcium folinate may be administered by IV infusion in doses of up to 75 mg within 12 hours, followed by 12 mg IM every 6 hours for 4 doses. When average doses of methotrexate appear to have an adverse effect, 6 to 12 mg of calcium folinate may be given IM every 6 hours for 4 doses.

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

PHARMACEUTICAL PARTICULARS

List of excipients

Core
Cellulose, microcrystalline
Povidone
Lactose monohydrate
Maize starch
Starch, pregelatinised
Silica, colloidal anhydrous
Magnesium stearate
Talc

Coating
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Quinoline yellow aluminium lake E104
Sunset yellow FCF aluminium lake E110

Shelf life

36 months.

Storage conditions

Do not store above 30 ºC. Keep the blister in the outer carton in order to protect from light.

Store in the original package in order to protect from moisture.

Keep out of the reach and sight of children.

Presentation

Cardboard box containing Aluminium-PVC/PVDC blisters of 10 film-coated tablets. Pack size of 100 film-coated tablets.

Manufacturer

Remedica Ltd.
Aharnon Str., Limassol Industrial Estate, 3056 Limassol, Cyprus

Product registrant

Goldplus Universal Pte Ltd
103 Kallang Avenue #06-02, Singapore 339504

Date of revision of the text