PRODUCT MONOGRAPH

[Pr] ratio-METHOTREXATE SODIUM

Methotrexate sodium

Tablets 2.5 mg USP

Antimetabolite

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Date of Preparation:
June 17, 2013

Submission Control No: 165513

Table of Contents

ratio-METHOTREXATE SODIUM

Methotrexate sodium Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets: 2.5 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Two major fields of indication exist for **ratio-METHOTREXATE SODIUM**:

- Neoplastic diseases
- Disease Modifying Antirheumatic Drug.

Neoplastic Diseases

- Choriocarcinoma: Methotrexate - as single chemotherapy or in combination with other drugs.
- Intermediate-, or high-grade Non-Hodgkin's Lymphoma as part of ProMACE-CytaBOM, ProMACE-MOPP, and Magrath protocols.
- Acute Lymphoblastic Leukemia - as maintenance therapy.
- Head and Neck Cancer - in combination with other chemotherapies.
- Metastasis of unknown primary - as palliative combination chemotherapy.
- Bladder Cancer (advanced) - as part of M-VAC Regimen.
- Burkitt's lymphoma.
- Advanced stages of childhood lymphoma (III and IV, St. Jude's Childrens' Research Hospital Staging System).
- Advanced cases of mycosis fungoides (cutaneous T-cell lymphoma)

Disease Modifying Antirheumatic Drug (DMARD)

The use of **ratio-METHOTREXATE SODIUM** as a DMARD in the following diseases where standard therapeutic interventions fail:

- Severe disabling psoriasis/psoriatic arthritis
- Severe disabling rheumatoid arthritis (RA)
- Severe, disabling seronegative arthritides.

In the treatment of psoriasis, **ratio-METHOTREXATE SODIUM** should be restricted to severe recalcitrant, disabling psoriasis, which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established after dermatologic consultation.

Geriatrics:
The clinical pharmacology of **ratio-METHOTREXATE SODIUM** has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Pediatrics:
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to **ratio-METHOTREXATE SODIUM** or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section.

- Pregnancy: **ratio-METHOTREXATE SODIUM** can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. **ratio-METHOTREXATE SODIUM** is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus.

- Women of childbearing potential should not be started on **ratio-METHOTREXATE SODIUM** 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 **ratio-METHOTREXATE SODIUM**. The optimal time interval between the cessation of **ratio-METHOTREXATE SODIUM** treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year. (See WARNINGS AND PRECAUTIONS.)

- Because of the potential for serious adverse reactions from **ratio-METHOTREXATE SODIUM** in breast fed infants, it is contraindicated in nursing mothers.

- **ratio-METHOTREXATE SODIUM** formulations and diluents containing preservatives must not be used for intrathecal, intraventricular, or high dose **ratio-METHOTREXATE SODIUM** therapy.

- **ratio-METHOTREXATE SODIUM** is contraindicated in patients with psoriasis or rheumatoid arthritis in the following situations:

    - Alcoholism, alcoholic liver disease or other chronic liver disease.

    - Overt or laboratory evidence of immunodeficiency syndromes.

    - Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anaemia.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **ratio-METHOTREXATE SODIUM** should be used only by physicians whose knowledge and experience includes the use of antimetabolite therapy. (See Indications and Clinical Use)
- Serious Toxic Reactions (See General section below)
- Use in pregnancy: Methotrexate has been reported to cause fetal death and/or congenital anomalies (See Special Populations, Pregnant Women section below). Pregnant patients with psoriasis or rheumatoid arthritis should not receive **ratio-METHOTREXATE SODIUM** (see CONTRAINDICATIONS).

General

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasized to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis.

Fatal toxicities related to intravenous dosing miscalculation have been reported. Special attention must be given to dose calculation.

Because of the possibility of serious toxic reactions (which can be fatal), **ratio-METHOTREXATE SODIUM** should be used only in life-threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. Deaths have been reported with the use of methotrexate sodium in the treatment of malignancy, psoriasis and rheumatoid arthritis. Because of the possibility of serious toxic reactions the patient should be informed by the physician of the risks involved and should be under a physician's constant supervision.

ratio-METHOTREXATE SODIUM has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on **ratio-METHOTREXATE SODIUM** closely. Most adverse reactions 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 hemodialysis with a high-flux dialyzer (See Overdosage). If **ratio-METHOTREXATE SODIUM** therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

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

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate sodium (usually in high dosage) along with nonsteroidal anti-inflammatory drugs (NSAlDs). (See Drug Interactions).

Bone marrow and mucosal toxicity of **ratio-METHOTREXATE SODIUM** depend on: dose and duration of exposure of high levels (>$2x10^{-8}$ mol/L (0.02 micromolar)) of **ratio-METHOTREXATE SODIUM**. Since the critical time factor has been defined for these organs as being 42 hours in humans, this has the following implications:

- when drug levels exceeding (2 x 10^{-8} mol/L (0.02 micromolar)) the above for >42 hours may forecast significant toxicity;
- when toxicity can be minimized by appropriate administration of Leucovorin Calcium;

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

ratio-METHOTREXATE SODIUM should be used with extreme caution in the presence of debility.

Carcinogenesis and Mutagenesis

Malignant lymphomas, which may regress following withdrawal of **ratio-METHOTREXATE SODIUM,** may occur in patients receiving low-dose **ratio-METHOTREXATE SODIUM** and, thus, may not require cytotoxic treatment. Discontinue **ratio-METHOTREXATE SODIUM** first and, if the lymphoma does not regress, appropriate treatment should be instituted.

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

No controlled human data exist regarding the risk of neoplasia with methotrexate sodium. Methotrexate sodium has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate sodium causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Assessment of the carcinogenic potential of methotrexate sodium is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. Benefit should be weighed against this potential risk before using **ratio-METHOTREXATE SODIUM** alone or in combination with other drugs, especially in children or young adults.

Also, see Toxicology.

Gastrointestinal

If vomiting, diarrhea, or stomatitis occur, resulting in dehydration, **ratio-METHOTREXATE SODIUM** should be discontinued until recovery occurs. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, haemorrhagic enteritis and death from intestinal perforation may occur. **ratio-METHOTREXATE SODIUM** should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic

ratio-METHOTREXATE SODIUM should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. Methotrexate sodium may produce marked bone marrow depression, with resultant anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting haematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC $<3000/mm^3$) was seen in 2 patients, thrombocytopenia (platelets $<1000,000/mm^3$) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, **ratio-METHOTREXATE SODIUM** should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases,

ratio-METHOTREXATE SODIUM should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic/Biliary/Pancreatic

ratio-METHOTREXATE SODIUM has the potential for acute and chronic hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after methotrexate sodium administration and are usually not a reason for modification of **ratio-METHOTREXATE SODIUM** therapy. Liver enzyme elevations are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity. 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. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. 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. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

ratio-METHOTREXATE SODIUM has caused reactivation or worsening of hepatitis B and C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of **ratio-METHOTREXATE SODIUM**. Prior to treatment with **ratio-METHOTREXATE SODIUM**, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection. **ratio-METHOTREXATE SODIUM** is not recommended for patients with active or chronic hepatitis B or C infection.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing, but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy.

The usual recommendation is to obtain a liver biopsy : 1) before the start of therapy or shortly after initiation of therapy (4-8 weeks); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of 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 pre-therapy. Although these mild changes are usually not a reason to avoid or discontinue **ratio-METHOTREXATE SODIUM** therapy, the drug should be used with caution.

Clinical experience with liver disease in rheumatoid arthritis is limited, but the same risk factors

would be anticipated. Liver function tests are also usually not reliable predictors of histological changes in this population.

In rheumatoid arthritis, advanced age at first use of **ratio-METHOTREXATE SODIUM**, and increasing duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving **ratio-METHOTREXATE SODIUM** 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), **ratio-METHOTREXATE SODIUM** may be continued and the patient monitored according to the recommendations listed above. **ratio-METHOTREXATE SODIUM** 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).

There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies 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 are 64 (7%) cases of fibrosis and 1 (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.

Immune

ratio-METHOTREXATE SODIUM 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.

Immunization may be ineffective when given during **ratio-METHOTREXATE SODIUM** therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Information for Patients

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

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity.
Patients should be informed of the potential benefit and risk in the use of **ratio-METHOTREXATE SODIUM**. The risk of effects on reproduction should be discussed with both male and female patients taking **ratio-METHOTREXATE SODIUM**.

Neurologic

There have been reports of leukoencephalopathy following intravenous administration of Methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous Methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leukoencephalopathy has also been reported in patients with osteosarcoma who received repeated doses of high-dose methotrexate sodium with leucovorin rescue even without cranial irradiation. There are also reports of leukoencephalopathy in patients who received low oral doses (4-8 mg/week) of methotrexate therapy for rheumatoid arthritis or psoriatic arthritis.

Discontinuation of **ratio-METHOTREXATE SODIUM** does not always result in complete recovery.

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

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given methotrexate in combination with cytarabine.

Renal

ratio-METHOTREXATE SODIUM therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong methotrexate sodium elimination. Methotrexate sodium may cause renal damage that may lead to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate sodium and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate sodium and creatinine levels are essential for safe administration.

Respiratory

Methotrexate sodium induced lung disease, including acute or chronic interstitial pneumonitis is a potentially dangerous lesion, which may occur at any time during therapy and which has been reported at low doses. It is not always fully reversible and fatalities have been reported. Cases of pleural effusion with or without interstitial pneumonitis have also been reported at any time during therapy at low doses. Pulmonary symptoms (especially a dry, nonproductive cough) or a non-specific pneumonitis occurring during **ratio-METHOTREXATE SODIUM** therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate sodium induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

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

Sexual Function/Reproduction

Methotrexate sodium causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

See Toxicology.

Skin

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, (Lyell's Syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal **ratio-METHOTREXATE SODIUM** administration. Reactions were noted after single or multiple, low, intermediate or high doses of **ratio- METHOTREXATE SODIUM** in patients with neoplastic and non-neoplastic diseases. Recovery has been reported with discontinuation of therapy.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of **ratio-METHOTREXATE SODIUM**.

Special Populations

Pregnant Women:

ratio-METHOTREXATE SODIUM can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. Methotrexate sodium is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus.

Women of childbearing potential should not be started on **ratio-METHOTREXATE SODIUM** 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 **ratio-METHOTREXATE SODIUM**. The optimal time interval between the cessation of **ratio-METHOTREXATE SODIUM** treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year.

Nursing Women:

Because of the potential for serious adverse reactions from **ratio-METHOTREXATE SODIUM** in breast fed infants, **ratio-METHOTREXATE SODIUM** is contraindicated in nursing mothers.

Pediatrics:

Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Fatal toxicities related to intravenous dosing miscalculation have occurred. Special attention must be given to dose calculation.

Geriatrics:

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasized to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis.

The clinical pharmacology of **ratio-METHOTREXATE SODIUM** has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Monitoring and Laboratory Tests

General:

Patients undergoing **ratio-METHOTREXATE SODIUM** therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count (CBC) with differential and platelet counts, hepatic enzymes, hepatitis B and C infection testing, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: haematology at least monthly, and hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate sodium blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Liver:

Liver biopsies prior to **ratio-METHOTREXATE SODIUM** therapy are not indicated routinely. Liver function tests (LFTs) should be determined prior to the initiation of therapy with **ratio-METHOTREXATE SODIUM** and they should be monitored regularly throughout therapy. A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient liver function test abnormalities are observed frequently after **ratio-METHOTREXATE SODIUM** administration and are usually not cause for modification of **ratio-METHOTREXATE SODIUM** therapy. Persistent liver function test abnormalities just prior to dosing and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.

Respiratory:

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

Serum Level Monitoring:

Serum methotrexate sodium level monitoring can significantly reduce **ratio-METHOTREXATE SODIUM** toxicity and mortality.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate sodium 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 sodium clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate sodium toxicity may not be reversible if adequate leucovorin rescue is delayed for more than 42 to 48 hours.

The method of monitoring methotrexate sodium concentrations varies from institution to institution. Monitoring of methotrexate sodium concentrations should include determination of a methotrexate sodium level at 24, 48, or 72 hours, and assessment of the rate of decline in methotrexate sodium concentrations (to determine how long to continue leucovorin rescue).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

- In general, the incidence and severity of acute side effects are related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate sodium to the target organs. The most serious reactions are discussed in Warnings and Precautions. That section should also be consulted when looking for information about adverse reactions with **ratio-METHOTREXATE SODIUM**.

- Some of the effects mentioned in this section, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

- The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Adverse Drug Reactions by Organ System

Adverse reactions that have been reported with methotrexate sodium are listed below alphabetically by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate sodium difficult.

Alimentary System: Gingivitis, stomatitis, enteritis, anorexia, nausea, vomiting, diarrhea, haematemesis, melena, gastrointestinal ulceration and bleeding, pancreatitis.

Cardiovascular: Pericarditis, and pericardial effusion (damage to heart, rarely), hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: Headaches, dizziness, drowsiness, speech impediment including dysarthria and aphasia; hemiparesis, paresis and convulsions have also occurred following administration of methotrexate sodium. Following low doses, there have been occasional reports of transient subtle

	cognitive dysfunction, mood alteration, or unusual cranial sensations, leukoencephalopathy, or encephalopathy.
Eye Disorders:	Conjunctivitis, blurred vision, serious visual changes of unknown etiology and transient blindness/vision loss.
Haematopoietic:	Methotrexate sodium can suppress haematopoiesis and cause anaemia, leukopenia, and/or thrombocytopenia. Hypogammaglobulinemia has been reported rarely (see Warnings and Precautions - Immune). Lymphadenopathy and lymphoproliferative disorders (including reversible), pancytopenia, neutropenia and agranulocytosis and eosinophilia have also been observed.
Hepatobiliary Disorders:	Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations, hepatic failure.
Infection:	There have been case reports of sometimes fatal sepsis, sepsis, opportunistic infections, including fatal infections in patients receiving methotrexate sodium therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included pneumonia, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex*, cytomegalovirus infection, including cytomegaloviral pneumonia, , reactivation of hepatitis B infection, worsening of hepatitis C infection.
Musculoskeletal, Connective Tissue, and Bone Disorders:	Stress fractures.
Pulmonary System:	Respiratory fibrosis, pharyngitis, interstitial pneumonitis deaths have been reported, pleural effusion and chronic interstitial obstructive pulmonary disease and alveolitis have occasionally occurred.
Skin:	Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome, skin necrosis, exfoliative dermatitis, and painful erosion of psoriatic plaques.
Urogenital System:	Severe nephropathy or renal failure, azotemia, dysuria, cystitis, haematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge and gynecomastia; infertility, abortion, fetal defects, loss of

libido/impotence. Proteinuria has also been observed.

Rarer reactions: Related to or attributed to the use of methotrexate sodium such as nodulosis, vasculitis, *herpes zoster*, sepsis, arthralgia/myalgia, diabetes, osteoporosis, sudden death, lymphoma, reversible lymphomas, tumour lysis syndrome, soft tissue necrosis, aplastic anaemia, fetal death and osteonecrosis. A few cases of anaphylactoid reactions have been reported.

Malignant lymphomas, which may regress following withdrawal of **ratio-METHOTREXATE SODIUM**, may occur in patients receiving low-dose **ratio-METHOTREXATE SODIUM**, and thus may not require cytotoxic treatment. Discontinue **ratio-METHOTREXATE SODIUM** first and, if the lymphoma does not regress, appropriate treatment should be instituted.

Other Adverse Drug Reactions

Adverse Reactions Reported in Rheumatoid Arthritis:

Incidence greater than 10%: elevated liver enzymes 15%, nausea/vomiting 10%.
Incidence 3% to 10%: stomatitis, thrombocytopenia.
Incidence 1% to 3%: rash/pruritus/dermatitis, alopecia, diarrhea, dizziness, leukopenia and pancytopenia.

Adverse Reactions in Psoriasis:

The adverse reaction rates reported are very similar to those in the rheumatoid arthritis studies. Rarely, painful psoriatic plaque erosions may appear.

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal hematologic and clinical chemistry findings are discussed in Warnings And Precautions – Monitoring and Laboratory Tests.

DRUG INTERACTIONS

Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction

(i.e., those identified as contraindicated).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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

In treating rheumatoid arthritis with **ratio-METHOTREXATE SODIUM**; acetyl salicylic acid (ASA), NSAIDs, and/or low dose steroids may be continued.

The possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate sodium. Combined use of **ratio-METHOTREXATE SODIUM** with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects.

Despite the potential interactions, studies of methotrexate sodium in patients with rheumatoid arthritis have usually included concurrent use of constant 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 that larger doses could lead to unexpected toxicity.

Leflunomide

ratio-METHOTREXATE SODIUM in combination with leflunomide may increase the risk of pancytopenia.

Drugs Highly Bound to Plasma Proteins

ratio-METHOTREXATE SODIUM is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides.

Probenecid

Renal tubular transport is also diminished by probenecid; use of **ratio-METHOTREXATE SODIUM** with this drug should be carefully monitored.

Nephrotoxic Drugs

Although not documented, other nephrotoxic drugs such as aminoglycosides, Amphotericin B, Cyclosporin could theoretically increase methotrexate sodium toxicity by decreasing its

elimination.

Penicillins and Sulfonamides

Penicillins and sulfonamides may reduce the renal clearance of methotrexate sodium; hematologic and gastrointestinal toxicity have been observed in combination with methotrexate sodium.

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 sodium or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. For example: Neomycin, Polymyxin B, Nystatin, Vancomycin decrease methotrexate sodium absorption, whereas Kanamycin increases methotrexate sodium absorption.

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

Theophylline

ratio-METHOTREXATE SODIUM may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with **ratio-METHOTREXATE SODIUM**.

Mercaptopurine

ratio-METHOTREXATE SODIUM increases the plasma levels of mercaptopurine. Combination of **ratio-METHOTREXATE SODIUM** and mercaptopurine may therefore require dose adjustment.

Vitamins
Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered Methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the cerebrospinal fluid (CSF) primarily as 5-methyl tetrahydrofolate and, in humans, remain 1 - 3 orders of magnitude lower than the usual Methotrexate concentrations following intrathecal administration.

In patients with rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce

methotrexate sodium toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B_{12} deficiency.

Folate deficiency states may increase methotrexate sodium toxicity.

Radiotherapy

ratio-METHOTREXATE SODIUM given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Hepatoxins

The potential for increased hepatotoxicity when methotrexate sodium 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 sodium and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Cytarabine

ratio-METHOTREXATE SODIUM given concomitantly with cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes (see Warnings And Precautions – Neurologic).

Drug-Food Interactions

The bioavailability of orally administered methotrexate sodium is reduced by food, particularly milk products.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Dosing Considerations

- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

- Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.

- **ratio-METHOTREXATE SODIUM** may only be administered by physicians experienced in the treatment of neoplasia. The oncologist should consult the current literature for the treatment regimen to be used. Typical dosages reported in the literature for the following malignancies are listed in the following section.

Recommended Dose and Dosage Adjustment

Bladder Cancer

Typical dosage regimens for bladder cancer are the CMV Regimen and the "M-VAC Regimen" which are represented in the following tables.

Table 1: CMV Regimen*

Drugs**	**Days**		
	1	2	8¶
Cisplatin‡		100	
Vinblastine	4		4
Methotrexate ***	30		30

* All doses in mg/m^2 with cycles repeated on day 22.
** Patients >70 years old receive 80% of all doses; if vomiting persists to day 8, no drug is given.
‡ For each cycle adjust cisplatin to 100% for Ccr >60 mL/min; 50% of dose for Ccr 50-60 mL/min; none for Ccr <50 mL/min.
*** No drug for a decrease on day 8 of >30 mL/min compared to day 1 or Ccr <50 mL/min or Cr >1.8 mg/dL.
¶ Major dose modifications for both drugs depending on myelosuppression.

Table 2: M-VAC Regimen*

Drugs	**Days**			
	1	2	15	22***
Methotrexate	30		30	30
Vinblastine		3	3	3
Doxorubicin		30**		
Cisplatin		70		

* All doses in mg/m^2 with cycles repeated every 28 - 32 days.
** Patients having prior pelvic irradiation equivalent to >2500 rad in 5 days, reduce the dose of doxorubicin 15 mg/m^2.
*** No doses given when the WBC <2500 cells/mm^3, platelets >100,000 cells/mm^3, or mucositis present.

Head and Neck Cancer

ratio-METHOTREXATE SODIUM remains the standard of therapy for patients with recurrent or metastatic disease. It has been given in a wide variety of doses and schedules (a few of which are represented in the table below).

Table 3: Methotrexate sodium Schedule **

25 - 50 mg every 4 to 7 days
80 mg/m^2 for 30 h every 2 wk with escalation to toxicity

** except from Devita, et al: CANCER 3rd Ed, p. 496

For palliation of patients with advanced, incurable disease and acceptable renal function, it is appropriate to begin oral **ratio-METHOTREXATE SODIUM** with weekly doses of 40-50 mg/m^2 or biweekly doses of 15 to 20 mg/m^2 and escalate the dose in weekly increments until either mild toxicity or therapeutic response is achieved.

Choriocarcinoma and similar trophoblastic diseases

ratio-METHOTREXATE SODIUM is administered orally or intramuscularly in doses of 15 to 30 mg daily for a 5 day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin hormone (beta-HCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of **ratio-METHOTREXATE SODIUM** after normalization of beta-HCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of **ratio-METHOTREXATE SODIUM** with other antitumour drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with **ratio-METHOTREXATE SODIUM** has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. **ratio-METHOTREXATE SODIUM** is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Lymphomas

In Burkitt's tumour, Stages I-II, methotrexate sodium has produced prolonged remissions in

some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate sodium is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate sodium given in doses of 0.625 to 2.5 mg/kg daily.

The treatment of choice for localized histologically aggressive lymphoma is primary combination chemotherapy with or without involved-field radiation therapy. Frequently used regimens for intermediate-, or high grade NHL that include methotrexate sodium include groups: the ProMACE/MOPP, ProMACE-CytaBOM, Magrath Protocols. Represented in the table below for example, is the ProMACE CytaBOM Regimen.

Table 4: ProMACE cytaBOM Regimen

ProMACE CytaBOM	Day 1	Day 8	Day 14	Days 15-21
Cyclophosphamide 650 mg/m^2 I.V.	x			No therapy
Doxorubicin 25 mg/m^2 I.V.	x			
Etoposide 120 mg/m^2 I.V.	x			
Cytarabine 300 mg/m^2 I.V.		x		
Bleomycin 5 mg/m^2 I.V.		x		
Vincristine 1.4 mg/m^2 I.V.		x		
Methotrexate 120 mg/m^2 I.V.		x with leucovorin rescue		
Prednisone 60 mg/m^2 PO	x----------	----------	----------x	
Co-trimoxazole 2 PO bid throughout 6 cycles of therapy				

In early stage childhood non-Hodgkin's lymphoma, **ratio-METHOTREXATE SODIUM** is used effectively in combination chemotherapy regimens.

Mycosis Fungoides (cutaneous T-cell lymphoma)

Therapy with **ratio-METHOTREXATE SODIUM** appears to produce clinical responses in up to 50% of patients treated, but chemotherapy is not curative. Dosage is usually 2.5 to 10 mg daily by mouth for several weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and haematologic monitoring. methotrexate sodium has also been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Leukemia

Acute lymphoblastic leukemia (ALL) 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.

Methotrexate sodium alone or in combination with steroids was used initially for induction of remission in ALL. More recently, corticosteroid therapy in combination with other antileukemic drugs or in cyclic combinations with methotrexate sodium included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate sodium in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate sodium in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: methotrexate sodium is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, re-induction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in ALL. The physician should be familiar with recent advances in antileukemic therapy.

Psoriasis and Rheumatoid Arthritis

Dosing Considerations

- Refer to Neoplastic Diseases – Dosing Considerations

- The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Warnings And Precautions - Information for Patients.)

- All dosage 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 (see Adverse Reactions). Maximal myelosuppression usually occurs in seven to ten days

Recommended Dose and Dosage Adjustment

Psoriasis

Recommended Starting Dose Schedules:
- Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate sodium may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis

Recommended Starting Dosage Schedules:

1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

Use in Patients with Renal Impairment

Table 5: Dose Adjustments in Patients with Renal insufficiency

Creatinine Clearance (mL/min)	% Standard Dose to Administer
>80	Full Dose
80	75
60	63
50	56
<50	Use alternative therapy

OVERDOSAGE

In postmarketing experience, overdose with methotrexate sodium has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, 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 anemia were also reported.

Discontinue or reduce dosage at the first sign of ulceration or bleeding, diarrhea, or marked depression of the haematopoietic system. Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of **ratio-METHOTREXATE SODIUM**. Leucovorin administration should begin as promptly as possible. As the time interval between **ratio-METHOTREXATE SODIUM** administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate sodium concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate sodium and / or its metabolites in the renal tubules. Generally, neither standard hemodialysis nor peritoneal dialysis has been shown to improve methotrexate sodium elimination. However, effective clearance of methotrexate sodium has been reported with acute, intermittent hemodialysis using a high-flux dialyzer.

There are published case reports of intravenous carboxypeptidase G2 treatment to hasten clearance of methotrexate sodium in cases of overdoses.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methotrexate sodium is a folate antagonist.

Methotrexate sodium inhibits dihydrofolate reductase (DHFR), the enzyme that reduces folic acid to tetrahydrofolic acid. Tetrahydrofolate must be regenerated via the DHFR-catalyzed reaction in order to maintain the intracellular pool of tetrahydrofolate one-carbon derivatives for both thymidylate and purine nucleotide biosynthesis. The inhibition of DHFR by folate antagonists (methotrexate) results in a deficiency in the cellular pools of thymidylate and purines and thus in a decrease in nucleic acid synthesis. Therefore, methotrexate sodium interferes with DNA synthesis, repair, and cellular replication.

Methotrexate sodium is most active against rapidly multiplying cells, because its cytotoxic effects occur primarily during the S phase of the cell cycle. Since cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate sodium may impair malignant growth without irreversible damage to normal tissues. As a result, actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to DHFR inhibition effects of methotrexate sodium.

The cytotoxicity of methotrexate sodium results from three important actions: inhibition of DHFR, inhibition of thymidylate synthase, and alteration of the transport of reduced folates. The affinity of DHFR to methotrexate sodium is far greater than its affinity for folic acid or dihydrofolic acid, therefore, large doses of folic acid given simultaneously will not reverse the affects of methotrexate sodium. However, Leucovorin calcium, a derivative of tetrahydrofolic acid may block the effects of methotrexate sodium if given shortly after the antineoplastic agent.

Methotrexate sodium has immunosuppressive activity. This may be a result of inhibition of lymphocyte multiplication. The mechanisms of action in the management of rheumatoid arthritis of the drug is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.

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 sodium to control the psoriatic process.

Pharmacokinetics

Absorption:

Orally administered methotrexate sodium is absorbed rapidly in most, but not all patients and reaches peak serum levels in one to four hours. Methotrexate sodium is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

Distribution:

Methotrexate sodium in serum is approximately 50% protein bound. After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate sodium does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally.

Metabolism:

After absorption, methotrexate sodium undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate sodium by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate syntheses. Small amounts of methotrexate sodium polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumours. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. methotrexate sodium is partially metabolized by intestinal flora after oral administration.

Excretion:

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. Excretion of single daily doses occurs through the kidneys in amounts from 80% to 90% within 24 hours. Repeated doses daily result in more sustained serum levels and some retention of methotrexate sodium over each 24-hour period, which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate sodium is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate sodium does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally.

The terminal half-life reported for methotrexate sodium is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2).
Methotrexate sodium clearance rates vary widely and are generally decreased at higher doses.

Special Populations and Conditions

Nursing Women:

Methotrexate sodium has been detected in human breast milk and is contraindicated during breast-feeding. The highest breast milk to plasma concentration ratio reached was 0.08:1.

STORAGE AND STABILITY

Keep in a safe place out of the reach of children.

Store at (15°C -30°C). Protect from light.

SPECIAL HANDLING INSTRUCTIONS

General:

Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects. Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs.

Safe Handling and Disposal:

ratio-METHOTREXATE SODIUM is a potent anti-neoplastic drug. Good medical practice will minimize exposure of persons involved with frequent handling of this drug as outlined below:

Handling:

1. **ratio-METHOTREXATE SODIUM** tablets have no vesicant properties and do not show acute toxicity on topical contact with the skin or mucous membranes. However, persons involved with handling cytotoxic drugs should avoid contact with skin and inhalation of airborne particles.
2. Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal:

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All materials for disposal which have come in contact with methotrexate sodium should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. Place container and tablets in a plastic bag, seal and mark as hazardous waste. Incinerate at 1000°C or higher.

4. If incineration is not available, rinse all materials for disposal which have come in contact with Methotrexate sodium solutions with water and discard in the sewer system with running water.

Dissolve tablets in a suitable quantity of normal sodium hydroxide (40 g per litre of water*) and discard in the sewer system with running water.

* Use appropriate safety equipment such as goggles and gloves while working with sodium hydroxide, since it can cause severe burns.

Cleaning:

Non-disposable equipment that has come in contact with Methotrexate sodium solutions may be rinsed with water and washed thoroughly with soap and water.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag; absorb remains with gauze pads or towels; wash area with water and absorb with gauze or towels again and place in bag; seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in cleanup should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Medicinal ingredients: Methotrexate

Non-medicinal ingredients: Corn Starch, Lactose, Magnesium Stearate, Dye Free.

Availability of Dosage Forms

ratio-METHOTREXATE SODIUM is available in the following dosage form:

Tablets :

Each round, yellow, scored tablet, engraved ‘2.5’ and ‘M1’ contains 2.5 mg of methotrexate sodium. Available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

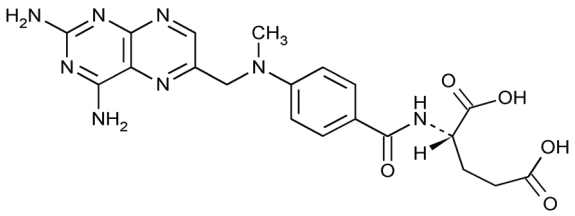
Drug Substance

Proper name: Methotrexate

Chemical name: N-[4-[[(2,4-diamino-6-pteridinyl)methylamino]benzoyl]-L-glutamic acid

Molecular formula and molecular mass: $C_{20}H_{22}N_8O_5$ (454.45 g/mol)

Structural formula:



Physicochemical properties:

Physical Form: A yellow to orange-brown crystalline powder. Contains not more than 12% water. Methotrexate sodium is a mixture of 4-amino-10-methylfolic acid and closely related compounds and is equivalent to not less than 94.0% of $C_{20}H_{22}N_8O_5$ calculated on the anhydrous basis. The parental solution is prepared with the sodium salt, but potency is always expressed on the basis of the acid.

Solubility: Practically insoluble in water, chloroform, ether and alcohol, but freely soluble in dilute solutions of mineral acids, alkali hydroxides and carbonates.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate sodium is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The bioavailability of orally administered methotrexate sodium is reduced by food, particularly milk products. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Methotrexate sodium is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate sodium competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate sodium in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate sodium does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

After absorption, methotrexate sodium undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate syntheses. Small amounts of methotrexate sodium polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumours. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate sodium is partially metabolized by intestinal flora after oral administration.

Half-life

The terminal half-life reported for methotrexate sodium is approximately three to ten hours for patients receiving treatment for psoriasis, rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate sodium, the terminal half-life is eight to fifteen hours.

Excretion

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate sodium serum levels. Excellent correlation has been reported between methotrexate sodium clearance and endogenous creatinine clearance.

Methotrexate sodium clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate sodium toxicity. It has been postulated that the toxicity of methotrexate sodium for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate sodium serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate sodium plasma

elimination. Pharmacokinetic monitoring of methotrexate sodium serum concentrations may help identify those patients at high risk for methotrexate sodium toxicity and aid in proper adjustment of leucovorin dosing.

TOXICOLOGY

The acute toxicity (LD_{50}) of methotrexate sodium in mice ranges from 65 to 70 mg/kg intravenously and 45 to 90 mg/kg intraperitoneally.

The acute oral toxicity (LD_{50}) in rats is 317 mg/kg; subcutaneously, it is 58 mg/kg and intraperitoneally it ranges from 80 to 464 mg/kg.

In a 22 month carcinogenicity study in rats that received methotrexate sodium at doses of 0.1, 0.2 and 0.4 mg/kg/day, 5 days/week every other week, little or no effect of the drug was observed. It has been concluded that methotrexate sodium is apparently remarkably free from toxic effects when otherwise lethal doses are administered utilizing an intermittent dosage schedule providing for a recovery period of 9 days. For example, daily oral doses of 0.4 mg/kg are lethal doses both in dogs and rats when administered for up to two weeks; when 0.5 mg/kg and 0.4 mg/kg doses, respectively, were administered daily five times a week every other week for three months to dogs and ten months to rats, they were found to be essentially without toxicity.

Methotrexate sodium is often used clinically in doses that are nearly toxic and may cause severe depression of all blood cellular elements. Constant supervision is recommended and signs of gastrointestinal ulceration and bleeding, including bleeding from the mouth, bone marrow depression, primarily of the white cell series and alopecia are indications of toxicity. In general, toxicity is in direct proportion to dose and exposure time to methotrexate sodium.

Toxicity of methotrexate sodium to the bone marrow and gastrointestinal epithelium is not so much dependent on dosage as on the duration of exposure of these organs to the drug and its extracellular (plasma) concentration. For bone marrow and gastrointestinal tract, the critical time factor has been defined as about 42 hours and the critical plasma concentration as $2X10^{-8}M$. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate sodium resulting in plasma levels in excess of $2X10^{-8}M$ circulating for greater than 42 hours will be toxic to both the bone marrow and gastrointestinal epithelium. This toxicity can be minimized by the appropriate administration of Leucovorin Calcium.

Methotrexate sodium may be hepatotoxic, particularly at high dosage and with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported.

REFERENCES

Anti-neoplastic Chemotherapy

1. Cannon GW. Pulmonary Toxicity of Methotrexate. In: William S. Wilke eds. Methotrexate Therapy in Rheumatic Disease. Marcel Dekker, Inc. 270 Madison Ave., New York, N.Y. 10016. 1989; 243-260.

2. Martindale: The Extra Pharmacopoeia. 29th Edition. James E.F. Reynolds ed. London Pharmaceutical Press 1989.

3. Evans AE, D'Angelo GJ, and Mitus A. Central Nervous System Complications of Children with Acute Leukemia. An Evaluation of Treatment Methods. J Pediat. 1964; 6:94-96.

4. Hertz R, Lewis J Jr., and Lipsett MB. Five Years' Experience with the Chemotherapy of Metastatic Choriocarcinoma and Related Trophoblastic Tumours in Women. Amer J Ob Gyn. 1961; 82:631-640.

5. Li MC. Trophoblastic Disease: Natural History, Diagnosis and Treatment. Ann. Int. Med. 1971; 74:102-112.

6. Krivit W, et al. Induction of Remission in Acute Leukemia of Childhood by Combination of Prednisone and either 6-mercaptopurine or Methotrexate. J Pediat. 1966; 68:965-968.

7. Acute Leukemia Group B.: Acute Lymphocytic Leukemia in Children. JAMA. 1969; 207: 923-928.

8. Burchenal JH. Chemotherapy for Leukemia. Postgrad. Med. 1970; 48:164-168.

9. Ziegler JL, et al. Treatment of Burkitt's Tumour with Cyclophosphamide. Cancer. 1970; 26:474-484.

10. Hryniuk WM and Bertino JR. Treatment of Leukemia with Large Doses of Methotrexate and Folinic Acid: Clinical Biochemical Correlates. J Clin Invest. 1969; 48:2140-2155.

11. Hersh EM, Wong VG, Henderson ES, and Freireich EJ. Hepatotoxic Effects of Methotrexate. Cancer. 1966; 19:600-606.

12. Dixon RL, Henderson ES, and Rall DP. Plasma Protein Binding of Methotrexate and its Displacement by Various Drugs. Fed. Proc. 1965; 24:454.

13. Pitman SW and Frei E. Weekly Methotrexate -Calcium Leucovorin rescue: Effect of alkalinization on nephrotoxicity: Pharmacokinetics in the CNS; and use in CNS Non-Hodgkin's lymphoma. Cancer Treat Reps. 1977; 61(4):695-701.

14. Rooney TW, Furst De. Comparison of toxicity in Methotrexate (MTX) treated rheumatoid arthritis (RA) patients also taking aspirin (ASA) or other NSAID. Abstract. Arthritis Rheum 29 Suppl 4:S76.

15. Aherne et al. Br Med J. 1978; 1:1097-1099.

16. Freisheim JH, Matthews DA. Dihydrofolate Reductases. Folate Antagonists as Therapeutic Agents. Academic Press Inc. 1984; 1:70-73.

17. DeVita Jr. LVT, Hellman S, Rosenberg SA. Clinical features of low-grade T-cell lymphomas. Cancer. Principles and Practice of Oncology. 4th. Ed. J.B. Lippincott Co., Philadelphia. pp. 1930-1935.

18. Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker AR, Kirkpatrick JA, Ayala AG, Shuster JJ, Abelson HT, Simone JV, Vietti TJ. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Eng J Med. 1986; 314(25):1600-1606.

19. Stark AN, Jackson G, Carey PJ, Arfeen S, Proctor SJ. Severe renal toxicity due to intermediate-dose Methotrexate. Department of Haematology, Royal Victoria Infirmary, Newcastle-upon-Tyne.

20. Evans WE, Christensen ML. Drug interactions with Methotrexate. J Rheumatol (Canada). 1985; Suppl 12 12:15-20.

21. Chabner BA, Collins JM. Cancer chemotherapy principles and practice. Philadelphia: Lippincott, 1990; 449-464.

22. Nyfors A. Benefits and adverse drug experiences during long-term Methotrexate treatment of 248 psoriatics.

Psoriasis Chemotherapy

23. Roenigk HH Jr, Maibach HI, and Weinstein GD. Use of Methotrexate in Psoriasis. Arch Derm. 1972; 105:363-365.

24. Roenigk HH Jr, Bergfeld WF, and Curits GH. Methotrexate for Psoriasis in Weekly Oral Doses. Arch Derm. 1969; 99:86-93.

25. Rees RB, Bennett JH, Maibach HI, and Arnold HL. Methotrexate for Psoriasis. Arch Derm. 1971; 103:33-38.

26. Roenigk HH Jr, Maibach HI, and Weinstein GD. Methotrexate Therapy for Psoriasis. Arch Derm. 1973; 108:35.

27. Weinstein GD. Methotrexate for Psoriasis. JAMA. 1973; 225:412.

28. McDonald CJ and Bertino JR. Parenteral Methotrexate in Psoriasis. Arch Derm. 1969; 100:655-668.

29. Weinstein GD. Methotrexate for Psoriasis. Dermatology Digest. 1973; 12:49-53.

30. Weinstein GD and Velasco J. Selective Action of Methotrexate on Psoriatic Epidermal Cells. J of Investigative Dermatology. 1972; 59: 121-127.

31. Coe RO and Bull FE. Cirrhosis Associated with Methotrexate Treatment of Psoriasis. JAMA. 1968; 206:1515-1520.

32. Weinstein CD, et al. Cooperative Study. Psoriasis-Liver Methotrexate Interactions. Arch Derm. 1973; 108:36-42.

33. Pearce, HP and Wilson, BB. Erosion of psoriatic plaques: An early sign of methotrexate toxicity. Am Acad Dermatol. 1996; 35:835-838.

NSAID Interactions

34. Adams JD and Hunter GA. Drug interaction in psoriasis. Aust J Derm. 1976; 17:3940.

35. Bloom EJ et al. Delayed clearance (CL) of Methotrexate (MTX) associated with antibiotics and anti-inflammatory agents. Abstract, Clin Res. 1986; 34, No. 2:560A.

36. Daly H. et al. Interaction between Methotrexate and non-steroidal anti-inflammatory drugs. Lancet. 1986; 557.

37. Daly H, et al. Methotrexate toxicity precipitated by azapropazone. Br J Derm. 1986; 114:733-735.

38. Doolittle GC, et al. Early-onset pancytopenia in two patients with rheumatoid arthritis receiving low-dose Methotrexate. Abstract 15C, Art. Rheum 1987; 30:S19, 1 Suppl.

39. Ellison NM, and Servi RJ. Acute renal failure and death following sequential intermediate-dose Methotrexate and 5-FU: A possible adverse effect due to concomitant Indomethacin administration. Cancer Treat Reps. 1985; 69(3):342-343.

40. Gabrielli A, et al. Methotrexate and non-steroidal anti-inflammatory drugs. Letter, Br Med J. 1987; 294:776.

41. Maiche AI. Acute renal failure due to concomitant action of Methotrexate and Indomethacin. Letter, Lancet. 1986; 1390.

42. Mandel MA. The synergistic effect of salicylates on Methotrexate toxicity. Plastic and Reconstructive Surg. 1976; 733-737.

43. Singh RR, et al. Fatal interaction between Methotrexate and Naproxen. Letter, Lancet. 1986; 1390.

44. Thyss A, et al. Clinical and pharmacokinetic evidence of a life-threatening interaction between Methotrexate and Ketoprofen. Lancet. 1986; 256-258.

Interaction with Radiotherapy

45. Turner SL, et al. Radical external beam radiotherapy of r333 squamous carcinomas of the oral cavity - Evaluation of the late morbidity and a watch policy for the clinically negative neck. Radiotherapy & Oncology. 1996; 41: 21-9.

Hemodialysis

46. Wall SM, et al. Effective clearance of methotrexate using high-flux hemodialysis membranes. Am J Kidney Dis. 1996; 28(6):846-854.

General

47. Kremer JM, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis & Rheumatol. 1994; 37(3):316-328.

48. Goodman TA, et al. Methotrexate: adverse reactions and major toxicities. Rheumatic Disease Clinics of North America. 1994; 20(2):513-28.

49. Tett SE, et al. Use of methotrexate in older patients. A risk-benefit assessment. Drugs & Aging. 1996; 9(6):458-71.

50. Said S, et al. Systemic treatment: methotrexate. Clinics in Dermatology. 1997; 15(5): 781-97.

51. Evans WE, et al. Applied Pharmacokinetics: Principles of therapeutic drug monitoring 3rd ed. Applied Therapeutics, Inc. Vancouver WA, 1992.

52. Green JA, et al. Drug interactions with cytotoxic agents. Cancer Topics. 1990; 7(11); 126-128.

53. Nierenberg W, et al. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide: a possible interaction. Arch-Dermatol. 1983; 119(6):449-50.

54. Squire EN, et al. Unexpected adverse effects of methotrexate (MTX) when used in the treatment of steroid-dependent asthma. Ann Allergy-Asthma-Immunol. 1996; 76(1): 106-(Abs).

55. Glynn Barnhart AM, et al. Effect of low-dose methotrexate on the deposition of glucocorticoids and theophylline. J. Allergy Clin Immunol. 1991; 88(2): 180-86.

56. Glynn Barnhart AM, et al. Effect of methotrexate on prednisolone and theophylline pharmacokinetics. Pharmacotherapy. 1990; 10(3):255.

57. Yokoo H, Nakazato Y, Harigaya Y, et.al. Massive myelinolytic leukoencephalopathy in a patient medicated with low-dose oral methotrexate for rheumatoid arthritis: an autopsy report. *Acta Neuropathol*. 2007;114:425-430.

58. Worthley S, McNeil J. Leukoencephalopathy in a patient taking low dose oral methotrexate therapy for rheumatoid arthritis. *J Rheumatol*. 1995;22:335-337.

59. Renard D, Westhovens R, Vandenbussche E, et.al. Reversible posterior leucoencephalopathy during oral treatment with methotrexate. *J Neurol.* 2004;251:226-228.

60. Raghavendra S, Nair MD, Chemmanam T, et.al. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate. *Eur J Neurol*. 2007;14:309-314.

61. Electronic communication from Yasuo Sugano, Labeling Group, PV Dept. Medical Affairs, WKK; 01 August 2008.

62. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systemic review of the literature. Ann Rheum dis. 2009;68;1094-1099

63. Product Monograph for Methotrexate manufactured by Wyeth Canada, dated April 21, 2011

.

PART III: CONSUMER INFORMATION

ratio-METHOTREXATE SODIUM
Methotrexate Sodium Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when **ratio-METHOTREXATE SODIUM** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **ratio-METHOTREXATE SODIUM**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ratio-METHOTREXATE SODIUM belongs to a group of medicines known as antimetabolites. It is used in high doses to treat certain types of cancers, including breast cancer, Non-Hodgkin's lymphoma and leukemia. At lower doses, it may also be used to treat severe psoriasis and severe rheumatoid arthritis. Methotrexate therapy is used to control psoriasis and rheumatoid arthritis but it will not cure them.

What it does:
ratio-METHOTREXATE SODIUM works by blocking an enzyme needed by body cells to live. This interferes with the growth of some cells, such as skin cells in psoriasis that are growing rapidly. In rheumatoid arthritis, **ratio-METHOTREXATE SODIUM** helps to reduce inflammation resulting in joint swelling. In cancer, **ratio-METHOTREXATE SODIUM** works by blocking an enzyme process in cancer cells so that they cannot grow. Some normal cells in the body may be affected as well.

When it should not be used:
Do not take **ratio-METHOTREXATE SODIUM** if you:
- Are allergic to any component of the drug
- Are pregnant. Methotrexate can cause harm to your unborn baby. Women of childbearing potential should not be started on ratio-METHOTREXATE SODIUM until pregnancy is excluded.
- Are breast feeding.
- Have psoriasis or rheumatoid arthritis and the following:
    - alcoholism (drink excessive alcohol)
    - chronic liver disease
    - immunodeficiency (resitance to infectious diseases is reduced)
    - blood disorders
    -

What the medicinal ingredient is:
Methotrexate (meth-o-TREX-ate).

What the important nonmedicinal ingredients are:
Corn starch, lactose and magnesium stearate; dye free.

What dosage forms it comes in:
2.5 mg tablets

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Methotrexate should be prescribed by a doctor who is experienced with the use of antimetabolite therapy.
- Methotrexate can cause serious toxic reactions which may result in death.
- Methotrexate can cause birth defect (deformed babies) or death of an unborn baby when used in pregnant women. Pregnant women with psoriasis or rheumatoid arthritis should not take Methotrexate

Before Using This Medicine
Before you start taking **ratio-METHOTREXATE SODIUM**, you should tell your doctor if you have any of the following conditions:
- have or have had any unusual or allergic reaction to **ratio-METHOTREXATE SODIUM.**
- are pregnant or planning to become pregnant. **ratio-METHOTREXATE SODIUM** can cause birth defects (deformed babies) or death of an unborn baby. Both male and female patients must use effective birth control methods all the time while taking **ratio-METHOTREXATE SODIUM** and a few months after the last dose of the drug. **ratio-METHOTREXATE SODIUM** may cause sterility (infertility), which could be permanent. Be sure to discuss this with your doctor before taking **ratio-METHOTREXATE SODIUM**. Tell your doctor right away if you think you have become pregnant while taking **ratio-METHOTREXATE SODIUM**.
- are breast-feeding or plan to breastfeed. **ratio-METHOTREXATE SODIUM** may cause serious side effects. Do not breastfeed while you are taking the drug
- have kidney problems
- have liver problems, including hepatitis B or hepatitis C infection
- have lung problems
- have problem with your immune system, or infections
- have gastrointestinal problems such as vomiting, diarrhea, mouth sores or inflammation, ulcer, or colitis (ulcer of intestines)
- have a skin disease
- have a neurologic disorder
- drink alcohol

ratio-METHOTREXATE SODIUM increases sensitivity to sunlight. Avoid sun exposure and do not use a sunlamp while taking this drug.

Precautions While Using This Medicine
- Do not take ratio-METHOTREXATE SODIUM daily or

more than the dose prescribed. ratio-METHOTREXATE SODIUM can cause serious toxic reactions which may result in death.
- Do not drink alcohol.
- Do not drive a car or operate machinery until you know how ratio-METHOTREXATE SODIUM affects you since the drug may cause dizziness and fatigue.
- Drink extra fluid to prevent kidney problems.
- Have regular blood tests to reduce the risk of infection or bleeding. ratio-METHOTREXATE SODIUM can lower the number of white blood cells and there is an increased risk of infection or bleeding.
- Talk to your doctor if you need a vaccination. Live vaccines may cause severe infections. Live vaccines or contact with any individual who has had a live vaccination should be avoided, since your ability to fight an infection (immune system) is decreased while taking ratio-METHOTREXATE SODIUM.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist what prescription and nonprescription medications, vitamins and herbal preparations you are taking or have recently taken. **ratio-METHOTREXATE SODIUM** may interact with the following drugs:
- nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylate (acetylsalicylic acid or ASA)
- drugs that may cause harm to the liver (leflunomide, azathioprine, sulfasalazine, retinoid)
- phenylbutazone
- phenytoin (to treat seizures)
- probenecid
- amphotericine B (may cause harm to kidneys)
- certain antibiotics such as penicillins, tetracycline, vancomycin, nystatin, neomycin, trimethoprim/ sulfamethoxazole, ciprofloxacin
- theophylline
- mercaptopurine
- folic acid or folinic acid
- cytarabine
- radiotherapy

The absorption of ratio-METHOTREXATE SODIUM when taken orally is reduced by food, particularly milk.

PROPER USE OF THIS MEDICATION

Take **ratio-METHOTREXATE SODIUM** only as directed by your doctor. Do not take more or less of it, and do not take it more often than your doctor ordered. The exact amount of medicine you need has been carefully worked out. Taking too much may increase the chance of side effects, while taking too little may not improve your condition. You should check with your doctor if you are not certain how to take the medication.

- **In most cases, ratio-METHOTREXATE SODIUM is taken once weekly; the prescribed dose is taken on a single day of the week.**
- **In some cases, your healthcare professional may instruct you to take ratio-METHOTREXATE SODIUM every 12 hours for 3 doses; you should only do this once a week, and should not take more than 3 doses each week.**
- **It should never be taken every day of the week.**
- **Taking ratio-METHOTREXATE SODIUM daily, or in a dose larger than prescribed can result in serious complications, often requiring hospitalization, and sometimes resulting in death. Taking even small doses of ratio-METHOTREXATE SODIUM daily for less than a week can result in serious consequences, including death.**
- Select a day of the week when you are most likely to remember to take ratio-METHOTREXATE SODIUM SODIUM, and take it on that same day each week.
- Each time you refill your prescription, check to see whether the dose and/or the number of tablets you need to take have changed.

ratio-METHOTREXATE SODIUM is often given together with certain other medicines. If you are using a combination of medicines, make sure that you take each one at the proper time and do not mix them. Ask your doctor or pharmacist to help you plan a way to remember to take your medicines at the right times.

While you are using **ratio-METHOTREXATE SODIUM**, your doctor may want you to drink extra fluids so that you will pass more urine. This will help the drug to pass from the body, and will prevent kidney problems and keep your kidneys working well.

If you vomit shortly after taking a dose of **ratio-METHOTREXATE SODIUM**, check with your doctor. You will be told whether to take the dose again or to wait until the next scheduled dose.

Usual dose:
The dose of **ratio-METHOTREXATE SODIUM** will be different for different patients. The dose that is used may depend on a number of things, including what the medicine is being used for, the patient's size, whether the medicine is being given by mouth or by injection, and whether or not other medicines are also being taken. If you are taking or receiving **ratio-METHOTREXATE SODIUM** at home, fallow your doctor's orders or the directions on the label. If you have any questions about the proper dose of **ratio-METHOTREXATE SODIUM**, ask your doctor.

Overdose:
- Immediately call your doctor or go to the nearest hospital emergency department or call your poison control centre.
- Do this even if you have no signs of discomfort.
- Always take the labelled medicine bottle with you, even if it is empty.

Missed Dose:

- If you missed a scheduled dose, contact your doctor for instruction.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with their needed effects, medicines like **ratio-METHOTREXATE SODIUM** can sometimes cause unwanted effects. Also, because of the way these medicines act on the body, there is a chance that they might cause other unwanted effects that may not occur until months or years after the medicine is used. These delayed effects may include certain types of cancer, such as leukemia. Discuss these possible effects with your doctor.

ratio-METHOTREXATE SODIUM commonly causes nausea and vomiting. Even if you begin to feel ill, do not stop using this medicine without first checking with your doctor. Ask your doctor for ways to lessen these effects.

The most common side effects include:

- Upset stomach, stomach pain, vomiting, nausea, loss of appetite, dizziness, chills and fever, diarrhea or sore on lips or mouth.
- A fall in the number of white blood cells. This may reduce your resistance to infection and increase your chances of cold sores, blood poisoning or swelling of blood vessels.
- Tiredness (fatigue).

Less common side effects are:

- Headaches, hair loss, mood changes, confusion, ringing in the ears, sore eyes, skin rashes, increased sensitivity to sunlight or unexplained weight loss.
- A fall in the number of other blood cells. This may increase your chances of bruising, bleeding or tiredness.
- Damage to the lungs.
- Harm to the unborn baby.
- Convulsions

Rarely and generally at higher doses for treatment of other diseases, **ratio-METHOTREXATE SODIUM** can cause other side effects including:

- Liver damage, kidney damage, pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine
- Fits, blurred vision, short term blindness
- Drowsiness, weakness
- Hoarseness
- Bloody vomit, black, tarry stools or pin-point red spots on the skin
- Reddening or whitening of the skin, acne, boils, itching yellow skin or eyes
- Impotence or loss of interest in sex, decreased fertility, abortion
- Diabetes, thinning of the bones, painful muscles and joints
- Low blood pressure
- Gastrointestinal ulcers

More rarely, it can cause:

- Skin rash and other skin disorders
- Cancer of lymph gland, sudden death
- Severe allergic reactions
- Leukoencephalopathy
- Damage to heart

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea, vomiting, abdominal pain,or mouth ulcers			T
	Sore throat, fever, chills, or swelling of glands		T	
Less Common	Chest pain, cough, shortness of breath or fever			T
	Unusual bleeding or bruising			T
	Severe headaches			T
Rare	Signs of severe allergic reaction: Skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, and/or a swollen face, lips, or tongue			T
	Pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine		T	
	Yellow colour of eyes or skin			T

*This is not a complete list of side effects. For any unexpected effects while taking **ratio-METHOTREXATE SODIUM**, contact your doctor or pharmacist.*

HOW TO STORE IT

To store this medicine:

- Keep out of the reach and sight of children.
- Do not handle ratio-METHOTREXATE SODIUM if you are pregnant or intend to become pregnant.
- Store it at room temperature and away from heat and direct light.
- Do not store **ratio-METHOTREXATE SODIUM** Tablets in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children
- Ask your pharmacist how to dispose of medicines no longer required.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be requested by contacting the sponsor, Teva Canada Limited at:
1-800-268-4127 ext. 1255005 (English)
1-877-777-9117 (French)
or druginfo@tevacanada.com

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9.

Last revised: June 17, 2013.