PRODUCT MONOGRAPH

PrAPO-METHOTREXATE

Methotrexate Tablets USP

2.5 mg (as methotrexate)

Antimetabolite and Antirheumatic

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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**.

INDICATIONS AND CLINICAL USE

APO-METHOTREXATE is indicated for Neoplastic diseases:

- Choriocarcinoma: Methotrexate ─ as single chemotherapy or in combination with other drugs.
- Acute Lymphoblastic Leukemia (ALL) •as maintenance therapy.
- Head and Neck Cancer •in combination with other chemotherapies.
- Metastasis of unknown primary •as palliative combination chemotherapy.
- 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).

APO-METHOTREXATE is indicated as a Disease Modifying Antirheumatic Drug (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, APO-METHOTREXATE 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 (≥65 years of age):
The clinical pharmacology of methotrexate 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 (<18 years of age):
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy. Therefore, APO-METHOTREXATE should not be used as a DMARD in pediatric patients.

CONTRAINDICATIONS

APO-METHOTREXATE is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- In patients with severe renal impairment including end stage renal disease with and without dialysis (see WARNINGS AND PRECAUTIONS, Renal, Special populations and DOSAGE AND ADMINISTRATION, Special populations).
- 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.
- In women of childbearing potential until pregnancy is excluded.
- In nursing mothers.
- In patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease.
- In patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes.
- In patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia.
- With nitrous oxide anesthesia (see **WARNINGS AND PRECAUTIONS: Renal** and **DRUG INTERACTIONS**: **Drug-Drug Interactions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- APO-METHOTREXATE should be used only by physicians whose knowledge and experience includes the use of antimetabolite therapy because of the possibility of serious toxic reactions (see **WARNINGS AND PRECAUTIONS**: **General**).

- Methotrexate has been reported to cause fetal death and/or congenital anomalies (see **WARNINGS AND PRECAUTIONS: Special Populations**: **Pregnant Women** section below). Therefore, use is contraindicated for women of childbearing potential until pregnancy is excluded and pregnant patients with psoriasis or rheumatoid arthritis (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, and that daily use of the weekly recommended dose has led to fatal toxicity.

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

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 APO-METHOTREXATE 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 APO-METHOTREXATE therapy is re-instituted, 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.

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 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 methotrexate levels.

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with non-steroidal anti-inflammatory drugs (NSAIDs) (see **DRUG INTERACTIONS**).

Bone marrow and mucosal toxicity depend on dose and duration of exposure of high levels ($>2x10^{-8}$ mol/L (0.02 micromolar)) of methotrexate. 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 2×10^{-8} mol/L (0.02 micromolar) for >42 hours may forecast significant toxicity
- when toxicity can be minimized by appropriate administration of Leucovorin Calcium.

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

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

Carcinogenesis and Mutagenesis

Malignant lymphomas may occur in patients receiving low-dose methotrexate. These lymphomas may regress following withdrawal of methotrexate without requiring treatment.

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

Gastrointestinal

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

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy as concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Hematologic

APO-METHOTREXATE should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. Methotrexate may produce marked bone marrow depression with resultant anemia, aplastic anemia, pancytopenia, leucopenia, neutropenia and/or thrombocytopenia. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100, 000/mm^3) in 6 patients, and pancytopenia in 2 patients.

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

Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after methotrexate

administration and are usually not a reason for modification of methotrexate 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.

Methotrexate 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 methotrexate. Prior to treatment with APO-METHOTREXATE, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection. APO-METHOTREXATE 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 APO-METHOTREXATE 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 methotrexate 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 APO-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), APO-METHOTREXATE may be continued and the patient monitored according to the recommendations listed above. APO-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).

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

APO-METHOTREXATE should be used with extreme caution in the presence of active infection, and is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes (see **CONTRAINDICATIONS**).

Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. Hypogammaglobulinemia has been reported rarely.

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 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 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 APO-METHOTREXATE 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 intravenous cytarabine.

Renal

Methotrexate is contraindicated in patients with severe renal impairment including end stage renal disease with and without dialysis (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**, Special populations). Methotrexate therapy in patients with mild and moderate renal impairment should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong methotrexate elimination. Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7- hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Nephritis has been reported on co-administration with nitrous oxide anesthesia in rheumatoid arthritis patients (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**: **Drug-Drug Interactions**).

Respiratory

Methotrexate-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 methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

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* should be considered.

Pulmonary alveolar haemorrhage has been reported with methotrexate. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Sexual Function/Reproduction

Methotrexate 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**). The risk of effects on reproduction should be discussed with both male and female patients taking APO-METHOTREXATE. (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 or intravenous methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic diseases, rheumatoid arthritis or psoriasis. 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 methotrexate.

Special Populations

Pregnant Women
APO-METHOTREXATE is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**: **Serious Warnings and Precautions**) and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy. Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman.

APO-METHOTREXATE is contraindicated in women of childbearing potential until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment (see **CONTRAINDICATIONS**). Pregnancy should be avoided if either partner is receiving APO-METHOTREXATE. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year. The risk of effects on reproduction should be discussed with both male and female patients taking APO-METHOTREXATE.

Nursing Women
APO-METHOTREXATE is contraindicated in nursing mothers because of the potential for serious adverse reactions from methotrexate in breast-fed infants.

Pediatrics (<18 years of age)
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Geriatrics (≥65 years of age)
The clinical pharmacology of methotrexate 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. Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity.

Renal Impairment

Methotrexate is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION,** Special populations).

Monitoring and Laboratory Tests

General
Patients undergoing APO-METHOTREXATE therapy should be informed of the early signs and symptoms of toxicity and closely monitored so that toxic effects are detected promptly. Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures. Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g., pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, and impaired renal function. Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate leucovorin rescue is delayed for more than 42 to 48 hours.

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

Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

During therapy of rheumatoid arthritis and psoriasis, monitor:

- **Hematologic:** Patients should have their blood tests checked at least monthly.

- **Hepatic:** Liver biopsies prior to APO-METHOTREXATE therapy are not indicated routinely. Liver function tests should be determined prior to the initiation of therapy with APO-METHOTREXATE and they should be monitored every 1 to 2 months. 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 APO-METHOTREXATE administration and are usually not cause for modification of APO-METHOTREXATE 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.

- **Renal:** Renal function should be monitored every 1 to 2 months.

- **Respiratory:** Pulmonary function tests may be useful if methotrexate-induced lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available.

During therapy of neoplastic disease:

More frequent monitoring is usually indicated during antineoplastic therapy for hematologic, hepatic, renal and respiratory.

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 to the target organs. The most serious reactions are discussed under **WARNINGS AND PRECAUTIONS** section. The most frequently reported adverse reactions include ulcerative stomatitis, leucopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

Adverse Drug Reactions by Organ System

Blood and lymphatic system disorders:	Leucopenia, anemia, aplastic anemia, thrombopenia, pancytopenia, agranulocytosis, lymphadenopathy and lymphoproliferative disorders (including reversible), neutropenia and eosinophilia have also been observed.
Cardiac disorders:	Pericarditis and pericardial effusion (damage to heart, rarely).
Eye disorders:	Conjunctivitis, blurred vision, serious visual changes of unknown etiology, and transient blindness/vision loss.
Gastrointestinal disorders:	Gingivitis, stomatitis, enteritis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, pancreatitis, intestinal perforation, non-infectious peritonitis, glossitis.
General disorders and administration site conditions:	Anaphylactoid reactions, vasculitis, fever, conjunctivitis, infection, sepsis, nodulosis, hypogammaglobulinaemia, and sudden death.
Hepatobiliary disorders:	Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations, hepatic failure.
Infection:	Other reported infections included

	nocardiosis, histoplasmosis, cryptococcosis, and disseminated *H. simplex*, cytomegalovirus infection, including cytomegaloviral pneumonia.
Metabolism and nutrition disorders:	Diabetes mellitus.
Musculoskeletal, connective tissue and bone disorders:	Stress fractures, soft tissue necrosis, osteonecrosis, arthralgia, myalgia and osteoporosis.
Neoplasms benign, malignant and unspecified (including cysts and polyps):	Tumour lysis syndrome. 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 APO-METHOTREXATE first and, if the lymphoma does not regress, appropriate treatment should be instituted.
Nervous system:	Cerebrospinal fluid pressure increased, neurotoxicity, arachnoiditis, paresthesia, headache, dizziness, drowsiness, speech impediment including dysarthria and aphasia; hemiparesis, paresis and convulsions. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations, leukoencephalopathy, or encephalopathy.
Renal and urinary disorders:	Renal failure, severe nephropathy or renal failure, azotemia, dysuria, cystitis, hematuria, urogenital dysfunction. Proteinuria has also been observed.
Reproductive system and breast disorders:	Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge and gynecomastia; infertility, abortion, fetal defects, loss of libido/impotence.
Respiratory, thoracic and mediastinal disorders:	Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, pulmonary fibrosis, pulmonary alveolar haemorrhage, *Pneumocystis carinii* pneumonia, pleural effusion. Dyspnea, chest pain, hypoxia, respiratory fibrosis, pharyngitis, and chronic

	interstitial obstructive pulmonary disease and alveolitis have occasionally occurred.
Skin disorders:	Erythema, pruritus, photosensitisation, petechiae, loss of hair, skin necrosis, exfoliative dermatitis, painful erosion of psoriatic plaques, herpes zoster, vasculitis, urticaria, pigmentary changes, acne, ecchymosis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), furunculosis and telangiectasia. Drug reaction with eosinophilia and systemic symptoms.
Vascular disorders:	Hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus), vasculitis.

Adverse Reactions Reported in Rheumatoid Arthritis:

- Alopecia (common)
- Diarrhea (common)
- Dizziness (common)
- Elevated liver enzymes (very common)
- Leucopenia (common)
- Nausea/vomiting (very common)
- Pancytopenia (common)
- Rash/pruritus/dermatitis (common)
- Stomatitis (common)
- Thrombocytopenia (common)

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

See **WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests** section.

Post-Market Adverse Drug Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse events have also been reported during post-marketing experience with methotrexate:

System Organ Class	Adverse Reaction

Infections and Infestations	Infections (including fatal sepsis); Pneumonia; *Pneumocystis carinii* pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; *H. simplex* hepatitis; Disseminated *H. simplex*; Cytomegalovirus infection (including cytomegaloviral pneumonia); Reactivation of hepatitis B infection; Worsening of hepatitis C infection
Blood and Lymphatic System Disorders	Agranulocytosis; Pancytopenia; Leukopenia; Neutropenia; Lymphadenopathy and lymphoproliferative disorders (including reversible); Eosinophilia; Anemia megaloblastic; Renal vein thrombosis; Lymphoma; Aplastic anemia; Hypogammaglobulinemia
Nervous System Disorders	CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness; Paresthesia
Respiratory, Thoracic and Mediastinal Disorders	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough; Plural effusion
Gastrointestinal Disorders	Intestinal perforation; Noninfectious peritonitis; Glossitis; Nausea; Pancreatitis
Hepatobiliary Disorders	Hepatic failure
Skin and Subcutaneous Tissue Disorders	Drug reaction with eosinophilia and systemic symptoms; Dermatitis; Petechiae
Musculoskeletal, Connective Tissue and Bone Disorders	Osteonecrosis
Renal and Urinary Disorders	Proteinuria
Pregnancy, Puerperium and Perinatal Conditions	Fetal death, Abortion
Reproductive System and Breast Disorders	Urogenital dysfunction
General Disorders and Administration Site Conditions	Pyrexia; Chills; Malaise; Fatigue; Anaphylactic reactions
Endocrine Disorders	Diabetes
Ophthalmologic Disorders	Transient blindness/vision loss

DRUG INTERACTIONS

Serious Drug Interactions

The use of nitrous oxide anesthesia with methotrexate is contraindicated (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**: **Renal** and **DRUG INTERACTIONS**: **Drug-Drug Interactions**)

Overview

In adults, oral absorption appears to be dose dependent. The bioavailability of orally administered methotrexate is reduced by food, particularly milk products. Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that undergo tubular secretion, can markedly increase methotrexate serum levels. Laboratory studies demonstrate that methotrexate may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol and phenytoin.

Drug-Drug Interactions

Non-steroidal Anti-inflammatory Drugs (NSAIDs)
NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic (including bone marrow suppression and aplastic anemia) and gastrointestinal toxicity. These drugs have been reported to reduce the tubular secretion of methotrexate, in an animal model, and may enhance its toxicity by increasing methotrexate levels.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of APO-METHOTREXATE. In treating rheumatoid arthritis with methotrexate, the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Despite the potential interactions, studies of methotrexate 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 toxicity.

Disease Modifying Antirheumatic drugs (DMARDs)
Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, or sulfasalazine has not been studied and may increase the incidence of adverse effects.

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

L-asparaginase
The administration of L-asparaginase has been reported to antagonize the effect of methotrexate.

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

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

Drugs Highly Bound to Plasma Proteins
Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs, such as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.

Packed Red Blood Cells
Care should be exercised whenever packed red blood cells and APO-METHOTREXATE are given concurrently. Patients receiving 24-hr methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged high serum-methotrexate concentrations.

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

Proton Pump Inhibitors
Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Concomitant use of PPIs and high-dose methotrexate should be avoided especially in patients with renal impairment. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

Psoralen Plus Ultraviolet Light (PUVA) Therapy

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

Nephrotoxic Drugs
Although not documented, other nephrotoxic drugs such as aminoglycosides, Amphotericin B, and Cyclosporin could theoretically increase methotrexate toxicity by decreasing its elimination.

Nitrous Oxide
The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis, neurotoxicity (with intrathecal administration of methotrexate) and nephritis (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS: Renal**). In case of accidental coadministration, this effect can be reduced by the use of leucovorin rescue.

Penicillins and Sulfonamides
Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity have been observed in combination with methotrexate. Use of APO-METHOTREXATE with penicillins should be carefully monitored.

Ciprofloxacin
Renal tubular transport is diminished by ciprofloxacin; use of APO-METHOTREXATE with this drug should be carefully monitored.

Oral Antibiotics
Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. For example: Neomycin, Polymyxin B, Nystatin and Vancomycin decrease methotrexate absorption, whereas Kanamycin increases methotrexate absorption.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Concurrent use of the anti-protozoal *pyrimethamine* may increase the toxic effects of methotrexate because of an additive antifolate effect.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with APO-METHOTREXATE.

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine. Combination of APO-METHOTREXATE and mercaptopurine may therefore require dose adjustment.

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the cerebrospinal fluid primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 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 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 toxicity.

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

Hepatoxins
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 APO-METHOTREXATE and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Cytarabine and other cytotoxic agents
Methotrexate given concomitantly with IV cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes (see **WARNINGS AND PRECAUTIONS: Neurologic**).

Combined use of methotrexate with other cytotoxic agents has not been studied and may increase the incidence of adverse effects.

Drug-Food Interactions
The bioavailability of orally administered methotrexate is reduced by food, particularly milk products.

Drug-Herb Interactions
The effects of herbal products on the pharmacokinetics of methotrexate have not been studied.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Use of alcohol with APO-METHOTREXATE is contraindicated (see **CONTRAINDICATIONS**). The effects of smoking, on the pharmacokinetics of methotrexate have not been specifically studied.

Some of the effects (e.g., dizziness and fatigue) may have an influence on the ability to drive or operate machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Neoplastic Diseases
- Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.
- APO-METHOTREXATE may only be administered by physicians experienced in the treatment of neoplasia. Typical dosages reported in the literature for the following

malignancies are listed in the following section.

Psoriasis and Rheumatoid Arthritis

- The patient should be fully informed of the risks involved and should be under constant supervision of the physician (see WARNINGS AND PRECAUTIONS).
- 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.
- 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.

Recommended Dose and Dosage Adjustments

Head and Neck Cancer

Methotrexate remains the standard of therapy for patients with recurrent or metastatic disease. It has been given in a wide variety of doses and schedules.

For palliation of patients with advanced, incurable disease and acceptable renal function, it is appropriate to begin oral methotrexate 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

Methotrexate is administered orally 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 methotrexate after normalization of beta-HCG are usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumour drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

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

Lymphomas

In Burkitt's tumour, Stages I-II, methotrexate 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 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 APO-METHOTREXATE 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.

Mycosis Fungoides (cutaneous T-cell lymphoma)
Therapy with methotrexate 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 hematologic monitoring.

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 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 included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate 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 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 is administered twice weekly by mouth in total weekly doses of 30 mg/m^2. 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.

Psoriasis
Recommended starting dose schedules:

- Weekly single oral dose schedule: 10 to 25 mg per week until adequate response is achieved.
- Divided oral dose schedule: 2.5 mg to 5.0 mg at 12-hour intervals for 3 doses, repeated weekly.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 25 mg/week should not ordinarily be exceeded.
Once optimal clinical response has been achieved, the dosage schedule should be reduced to the lowest possible effective dose and to the longest possible rest period.

Rheumatoid Arthritis
Recommended starting dosage schedules:

- Single oral doses of 7.5 mg once weekly.

- 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 gradually adjusted to achieve optimal clinical 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. Upon achieving the therapeutically desired result, dosage should be reduced gradually to the lowest possible effective maintenance dose. The optimal duration of therapy is unknown; limited data from long-term studies indicate that the initial clinical improvement is maintained for at least 2 years with continued therapy.

Special Populations

Renal Impairment
Methotrexate is excreted to a significant extent by the kidneys, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug. The table below provided recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide inter subject pK variability. Methotrexate is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS).

Table 1: 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

Pediatrics (<18 years of age)
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy (see **WARNINGS AND PRECAUTIONS**: **Special Populations**, **Pediatrics**).

Geriatrics (≥65 years of age)
Due to diminished hepatic and renal function as well as decreased folate stores in elderly population, relatively low doses (especially in rheumatoid arthritis and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity. See **Table 1** for reduced doses in oncology patients with renal impairment.

Missed Dose
If a scheduled dose is missed, contact your doctor for instructions.

OVERDOSAGE

Overdose with methotrexate has occurred with oral administration.

Reports of oral overdose indicate accidental daily administration instead of weekly. Symptoms commonly reported 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). There have been reports of death following chronic overdose in the self-administered dosage for rheumatoid arthritis and psoriasis. 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 hematopoietic system. Leucovorin is indicated to diminish the toxicity and counteract the effect of overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate 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 and/or its metabolites in the renal tubules. Generally, neither standard hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate 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 in cases of overdoses.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methotrexate is a folate antagonist.

Methotrexate 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 interferes with DNA synthesis, repair, and cellular replication.

Methotrexate 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 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.

The cytotoxicity of methotrexate 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 is far greater than its affinity for folic acid or dihydrofolic acid, therefore, large doses of folic acid given simultaneously will not reverse the effects of methotrexate. However, Leucovorin calcium, a derivative of tetrahydrofolic acid may block the effects of methotrexate if given shortly after the antineoplastic agent.

Methotrexate 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 are 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 to control the psoriatic process.

Pharmacokinetics

Absorption
Orally administered methotrexate is absorbed rapidly in most, but not all patients and reaches peak serum levels in 1 to 2 hours in adults and 0.67 to 4 hours in children. Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

Distribution
Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Methotrexate 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 0.8L/kg (40% to 80% of body weight). Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally.

Metabolism
At low doses, methotrexate does not appear to undergo significant metabolism; following high-dose therapy, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes.

These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate syntheses. Small amounts of methotrexate 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 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. Total clearance averages 12 L/h, but there is wide interindividual variation.

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

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2).

Methotrexate clearance rates vary widely and are generally decreased at higher doses.

Special Populations and Conditions

Nursing Women

Methotrexate 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.

Pediatrics
In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose-dependent and 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 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses.
In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours.

Geriatrics
The clinical pharmacology of methotrexate 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 (especially in RA and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity.

Renal Impairment
Since the renal excretion of methotrexate is the primary route of elimination with 80% to 90% of the single daily doses of methotrexate excreted through the kidneys within 24 hours, methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug.

Hepatic Impairment
Hepatic excretion of methotrexate is a minor route of elimination. However, the liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

STORAGE AND STABILITY

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

Store APO-Methotrexate between 15°C and 25°C. Keep the tablet container in the outer carton in order to 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.

Safe Handling and Disposal
Good medical practice will minimize exposure of persons involved with frequent handling of this drug as outlined below:

Handling

1. Methotrexate has no vesicant properties and does 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. Place container and tablets in a plastic bag, seal and mark as hazardous waste. Incinerate

at 1000ºC or higher.

Dissolve tablets in a suitable quantity of normal sodium hydroxide (40 g per liter 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 APO-METHOTREXATE 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 clean up should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

APO-METHOTREXATE (methotrexate tablets, USP 2.5 mg) is available in bottles of 100.

Composition
Each small, round, yellow, uncoated tablet, engraved M over 2.5 on one side, contains methotrexate 2.5 mg. There are no preservatives or colouring agents.

Non-medicinal Ingredients
Cornstarch, lactose, magnesium stearate, polysorbate 80, microcrystalline cellulose and starch pregelatinized.

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: An orange-brown crystalline powder. Methotrexate 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.

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

CLINICAL TRIALS

Study Demographics and Trial Design

Table 2: Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
	Controlled double-blind multicentre	Oral 18 weeks	n=189	N/A	N/A

One hundred eighty-nine patients with rheumatoid arthritis were entered into a prospective, controlled, double-blind, multicentre trial comparing placebo and methotrexate (Williams et al, 1985).

One hundred ten patients completed 18 weeks of therapy. Virtually all of these patients were on concomitant non-steroidal anti-inflammatory medication and some were also taking low dosages of corticosteroids.

Patients received either 2.5 mg tablets of methotrexate or identical placebo tablets. Therapy was initiated at 1 tablet 3 times per week, with doubling of dosage permitted after 6 weeks if judged to be in the patient's interests.

Although no remissions were seen, patients able to tolerate low-dose pulse methotrexate therapy were significantly improved, compared with patients receiving placebo therapy, for all clinical variables measured, including joint pain/tenderness and swelling counts, rheumatoid nodules, and patient and physician assessment of disease activity.

Study Results

Table 3: Number (%) Patients with Remission or Significant Improvement

Variable	Placebo	Methotrexate
Remission improvement	0	0
Pain/tenderness*	10 (11%)	30 (32%)
Swelling*	4 (4%)	20 (21%)
Patient assessment*	7 (7%)	10 (11%)
Physician assessment**	3 (3%)	9 (10%)

* N = 94 methotrexate, 89 placebo
** N = 95 methotrexate, 94 placebo

Comparative Bioavailability Studies

A comparative bioequivalence study of Wyeth* Methotrexate and Apotex APO-

METHOTREXATE in cancer patients demonstrated that the two products were bioequivalent (**Table 4**) based on the mean area under the time plasma concentration curve (AUC), time to reach peak concentration (T_{max}) and peak plasma valued (C_{max}).

Table 4: Pharmacokinetic indices for Apotex Inc. and Wyeth* Methotrexate Tablets

Methotrexate Tablets (1 x 2.5 mg) From measured data		
Parameter	**Apotex Methotrexate Tablets**	**Wyeth* Methotrexate Tablets**
AUC_T** (units)	530.2 ng·hrs/mL	539.8 ng·hrs/mL
C_{max}*** (units)	156.6 ng/mL	179.7 ng/mL
T_{max}**** (h)	0.75 hrs	0.94 hrs

* The registered owner of the innovator has since been changed from Wyeth to Pharmascience.
** AUC_T = Area under the plasma concentration – time curve
*** C_{max} = Maximum plasma or blood concentration
**** T_{max} = Time of maximum concentration

DETAILED PHARMACOLOGY

Human Pharmacokinetics

Absorption
Orally administered methotrexate is absorbed rapidly in most, but not all patients and reaches peak serum levels in 1 to 2 hours in adults; Oral absorption appears to be dose-dependent. At doses of 30 mg/m^2 or less, methotrexate 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. Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

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 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 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 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 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 does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally. High cerebrospinal fluid 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 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 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 is partially metabolized by intestinal flora after oral administration.

Half-Life
The terminal half-life reported for methotrexate 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, 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. Non-linear 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

serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate 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 toxicity. It has been postulated that the toxicity of methotrexate 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 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 plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing.

TOXICOLOGY

The acute toxicity (LD_{50}) of methotrexate in mice ranges from 65 to 70 mg/kg intravenously. In dogs, the intravenous dose of 50 mg/kg was lethal. The main targets after a single dose were the hemolymphopoietic system and gastrointestinal (GI) tract.

The acute oral toxicity (LD_{50}) in rats was 180 mg/kg; subcutaneously, it is 58 mg/kg. The tolerance to methotrexate in mice increased with age. The toxic effects after repeated administration of methotrexate were investigated in mice and rats. The main targets of methotrexate in the above animal species were the hemolymphopoietic system, GI tract, lung, liver, kidney, testes, and skin. The tolerance of mice to chronic methotrexate doses increased with age.

In a 22-month carcinogenicity study in rats that received methotrexate 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 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 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.

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

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PART III: CONSUMER INFORMATION

[Pr]APO-METHOTREXATE
Methotrexate Tablets USP
2.5 mg

Read this carefully before you start taking APO-METHOTREXATE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about APO-METHOTREXATE.

ABOUT THIS MEDICATION

What the medication is used for:
APO-METHOTREXATE belongs to a group of medicines known as antimetabolites. It is used to treat certain types of cancers, severe psoriasis and severe rheumatoid arthritis.

What it does:
APO-METHOTREXATE 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, APO-METHOTREXATE acts on the inflammatory cells that cause joint swelling. APO-METHOTREXATE therapy is used to control psoriasis and rheumatoid arthritis but it will not cure them. In cancer, APO-METHOTREXATE 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 APO-METHOTREXATE if you:

- Are allergic to any component of the drug
- Have severe kidney problems
- Are on dialysis
- Are pregnant. APO-METHOTREXATE can cause harm to your unborn baby. Women of childbearing potential should not be started on APO-METHOTREXATE until pregnancy is excluded.
- Are breast-feeding
- Have psoriasis or rheumatoid arthritis and the following:
  - alcoholism (drink excessive alcohol)
  - chronic liver disease
  - immunodeficiency (resistance to infectious diseases is reduced)
  - blood disorders
- Are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas.

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

What the important nonmedicinal ingredients are:
Cornstarch, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80 and starch pregelatinized.

What dosage forms it comes in:
Tablet: 2.5 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
APO-METHOTREXATE should be prescribed by a doctor who is experienced with the use of antimetabolite therapy.

- APO-METHOTREXATE can cause serious toxic reactions which may result in death.
- APO-METHOTREXATE can cause birth defects (deformed babies) or death of an unborn baby when used in pregnant women. Pregnant women with psoriasis or rheumatoid arthritis should not take APO-METHOTREXATE.

Before you use APO-METHOTREXATE, talk to your doctor or pharmacist if you have any of the following conditions:

- have or have had any unusual or allergic reaction to APO-METHOTREXATE
- are pregnant or planning to become pregnant. APO-METHOTREXATE 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 APO-METHOTREXATE and a few months

after the last dose of the drug. APO-METHOTREXATE may cause sterility (infertility), which could be permanent. Be sure to discuss this with your doctor before taking APO-METHOTREXATE. Tell your doctor right away if you think you have become pregnant while taking APO-METHOTREXATE
- are breast-feeding or plan to breast-feed. APO-METHOTREXATE may cause serious side effects. Do not breast-feed while you are taking the drug.
- have kidney disease
- have or have had 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 the intestines)
- Are dehydrated or have a lot of vomiting, diarrhea, or sweating.
- have a skin disease
- have a neurologic disorder
- drink alcohol

APO-METHOTREXATE 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 APO-METHOTREXATE more than the dose prescribed. APO-METHOTREXATE 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 APO-METHOTREXATE 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. APO-METHOTREXATE 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 APO-METHOTREXATE.

Methotrexate can cause sudden bleeding in the lungs. This is called **Pulmonary alveolar haemorrhage**. If you suddenly spit or cough up blood you must go to the hospital right away. You will need emergency care. This occurs in patients with some existing health problems. Some examples are rheumatic disorder (such as pain in your joints) or vasculitis such as swelling in an artery or vein.

INTERACTIONS WITH THIS MEDICATION

Talk to your healthcare professional about all the medicines you take or have recently taken, including any drugs, vitamins, minerals, natural supplements or alternative medicines. APO-METHOTREXATE may interact with the following drugs:

Do not take APO-METHOTREXATE if you are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas. When used together, they can cause:
- Myelosuppression (a condition in which the bone marrow cannot make enough blood cells)
- Mouth sores
- Inflammation of the mouth
- Inflammation of the kidneys
- Damage to the nervous system.

- Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylate (acetylsalicylic acid or ASA).
- Disease Modifying Antirheumatic drugs (DMARDs), such as gold, penicillamine, hydroxychloroquine, or sulfasalazine

- 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, pristinamycin, chloramphenicol
- Theophylline
- Mercaptopurine
- Folic acid or folinic acid
- Cytarabine and other chemotherapy agents
- Radiotherapy
- L-asparaginase, a drug used to treat cancer
- Proton pump inhibitors (PPI). They are drugs used to treat acid-related stomach problems. Some PPIs are omeprazole, esomeprazole and pantoprazole.
- Pyrimethamine, an anti-parasitic drug
- Nitrous oxide, an inhaled gas used to prevent pain during medical procedures
- Amiodarone, a drug used to treat abnormal heart rhythms
- Sulfonylureas, drugs used to lower blood sugar levels, aminobenzoic acid, sulfonamides, also known as "sulfa drugs"
- Packed red blood cells, used for blood transfusions
- PUVA therapy, a type of ultraviolet light treatment for severe skin conditions
- Triamterene, a drug used to reduce blood pressure and decrease swelling

The absorption of APO-METHOTREXATE is reduced by food, particularly milk.

PROPER USE OF THIS MEDICATION

Take APO-METHOTREXATE 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, APO-METHOTREXATE 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 APO-METHOTREXATE 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 when used to treat psoriasis or rheumatoid arthritis. As well, in most cases of cancer, Apo-Methotrexate should not be taken every day of the week.**
- **Taking APO-METHOTREXATE 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 APO-METHOTREXATE 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 APO-METHOTREXATE, 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.

APO-METHOTREXATE 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 APO-METHOTREXATE, 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 APO-METHOTREXATE, 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 APO-METHOTREXATE 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, and whether or not other medicines are also being taken. The doctor may decrease your dose if you have problems with your kidneys. If you are taking or receiving APO-METHOTREXATE at home, follow your doctor's orders or the directions on the label. If you have any questions about the proper dose of APO-METHOTREXATE, ask your doctor.

Overdose:

If you think you have taken too much APO-METHOTREXATE, contact your healthcare professional, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

- 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 APO-METHOTREXATE can 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.

APO-METHOTREXATE 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 sores 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, APO-METHOTREXATE 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 glands, sudden death
- Severe allergic reactions
- Leukoencephalopathy
- Damage to the heart

Methotrexate can cause abnormal test results. Your doctor will decide when to perform tests and will interpret the results. This includes blood and urine tests to check how your kidneys are working.

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			√
	Sore throat, fever, chills, or swelling of glands		√	
	Inflammation of the lungs: Persistent dry, non-productive cough, shortness of breath and fever.		√	
Less common	Chest pain, cough, shortness of breath or fever			√
	Unusual bleeding or bruising			√
	Severe headaches			√
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			
	Pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine		√	
	Yellow colour of eyes or skin			√
	Renal failure/kidney damage (inability of the kidneys to work properly): swelling of the hands, ankles or feet. Nausea, vomiting. Blood in the urine. Changes in frequency or amount of urine.			√
Unknown	**Gastrointestinal Related:** Severe abdominal pain, tenderness, chills, fever, nausea, vomiting, extreme thirst, difficulty passing urine or bowel movement			√
	Central Nervous System Related: Behaviour changes, decreased consciousness, headache, weakness, numbness, vision loss or double vision, seizures, vomiting, loss of memory			√
	DRESS (allergic reactions): Fever, rash, hives, swelling of eyes, lips or tongue			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Pulmonary alveolar haemorrhage: suddenly spit or cough up blood			√

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

To store this medicine:

- Keep out of the reach and sight of children.
- Store APO-METHOTREXATE between 15°C and 25°C, away from heat and direct light. Keep the tablet container in the outer carton in order to protect from light.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach and sight of children.

MORE INFORMATION

NOTE: This Consumer Information provides you with the most current information at the time of printing.

If you want more information about APO-METHOTREXATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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