PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-METHOTREXATE

Methotrexate Tablets

2.5 mg methotrexate (as methotrexate disodium), For Oral Use

USP

Antimetabolite

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montréal, Québec
H4P 2T4

www.pharmascience.com

Date of Authorization:
JUL 31, 1995

Date of Revision:
JAN 08, 2025

Submission Control Number: 285869

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Neurologic	01/2025

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-METHOTREXATE is indicated for Neoplastic diseases:

- Choriocarcinoma: Methotrexate – as single chemotherapy or in combination with other drugs.
- Acute Lymphoblastic Leukemia – 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'd Research Hospital Staging System).
- Advanced cases of mycosis fungoides (cutaneous T-cell lymphoma).

pms-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, pms-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.

1.1 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy. Therefore, pms-METHOTREXATE should not be used as a DMARD in pediatric patients.

1.2 Geriatrics

Geriatrics (≥65 years of age): Experience suggests that use in the geriatric population is associated with differences in safety (see 4.2 Recommended Dose and Dose Adjustment; and 7.1.4 Warnings and Precautions, Geriatrics).

2 CONTRAINDICATIONS

pms-METHOTREXATE is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, COMPOSITION AND PACKAGING.
- 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.
- In patients with severe renal impairment including end stage renal disease with and without dialysis (see 7 WARNINGS AND PRECAUTIONS, Renal, 7.1 Special Populations; and 6 DOSAGE AND ADMINISTRATION).
- With nitrous oxide anesthesia (see 7 WARNINGS AND PRECAUTIONS, Renal; and 9.4 Drug-Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- pms-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 7 WARNINGS AND PRECAUTIONS, General).

- Methotrexate has been reported to cause fetal death and/or congenital anomalies (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women). Therefore, use is contraindicated for women of childbearing potential until pregnancy is excluded and pregnant patients with psoriasis or rheumatoid arthritis (see 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

pms-METHOTREXATE should not be initiated in women of childbearing potential until pregnancy is excluded.

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.
- pms-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 7 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 8 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.

4.2 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 is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumour drugs has been reported as being useful.

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

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. pms-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 pms-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 2 times 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 dose 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:

Hepatic Impairment: pms-METHOTREXATE should be used with caution in patients with pre-existing liver damage or impaired hepatic function. Dose adjustments may be necessary, and liver function tests should be monitored regularly.

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. pms-METHOTREXATE is contraindicated in patients with severe renal impairment (see 2 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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 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.

4.5 Missed Dose

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

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	All Non-medicinal Ingredients
Oral	Tablets/ 2.5 mg methotrexate (as methotrexate disodium)	Corn Starch, Lactose, Magnesium Stearate, Sodium Hydroxide, Purified Water

Description

Each round, yellow, scored tablet, engraved “2.5” and “M1”, contains 2.5 mg methotrexate (as methotrexate disodium). Available in bottles of 100 tablets and in blister packages of 30 tablets (3 x 10).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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), pms-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 pms-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 5 OVERDOSAGE). If pms-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 pms-

METHOTREXATE (usually in high dosage) along with non-steroidal anti-inflammatory drugs (NSAIDs) (see 9 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.

pms-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 pms-METHOTREXATE alone or in combination with other drugs, especially in children or young adults (see 16 NON-CLINICAL TOXICOLOGY).

Driving and Operating Machinery

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

Gastrointestinal

If vomiting, diarrhea, or stomatitis occurs, resulting in dehydration, pms-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. pms-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 9.4 Drug-Drug Interactions).

Hematologic

pms-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, pms-METHOTREXATE should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, pms-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 pms-METHOTREXATE, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection. pms-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 pms-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 pms-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), pms-METHOTREXATE may be continued and the patient monitored according to the recommendations listed above. pms-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

pms-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 2 CONTRAINDICATIONS).

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

Monitoring and Laboratory Tests

General: Patients undergoing pms-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 pms-METHOTREXATE therapy are not indicated routinely. Liver function tests should be determined prior to the initiation of therapy with pms-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 pms-METHOTREXATE administration and are usually not cause for modification of pms-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.

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 (4-8mg/week) of methotrexate therapy for rheumatoid arthritis or psoriatic arthritis.

Discontinuation of pms-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 pms-METHOTREXATE in combination with intravenous cytarabine.

Progressive multifocal leukoencephalopathy (PML): Cases of progressive PML, including fatal cases, have been reported with methotrexate use. PML is a rare and often fatal demyelinating disease attributed to the presence within the CNS of the John Cunningham virus (JCV) and its reactivation in people with suppressed immune function. Health professionals should consider PML in patients with new or worsening neurological, cognitive, or behavioural signs or symptoms and should take appropriate diagnostic measures. If PML is suspected, further methotrexate dosing must be suspended. If PML is confirmed, methotrexate should be permanently discontinued.

Renal

Methotrexate is contraindicated in patients with severe renal impairment including end stage renal disease with and without dialysis (see 2 CONTRAINDICATIONS; and 4 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 2 CONTRAINDICATIONS; and 9.4 Drug-Drug Interactions).

Reproductive Health

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 period after cessation of therapy. Pregnancy should be avoided if either partner is receiving pms-METHOTREXATE. The optimal time interval between cessation of methotrexate treatment of either partner and pregnancy has not been 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 pms-METHOTREXATE (see 2 CONTRAINDICATIONS; 3 SERIOUS WARNINGS AND PRECAUTIONS BOX,; and 7.1.1 Pregnant Women).

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 nonspecific 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.

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.

7.1 Special Populations

7.1.1 Pregnant Women

pms-METHOTREXATE is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis (see 2 CONTRAINDICATIONS; and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX) 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 period after cessation of therapy. Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman.

pms-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 2 CONTRAINDICATIONS). Pregnancy should be avoided if either partner is receiving pms-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 pms-METHOTREXATE.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse 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 7 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.

Table 3: 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, hypogammaglobulinemia, 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.
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 (DRESS).
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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

8.5 Post-Market Adverse 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:

Table 4: Post-Market Adverse Reactions

System Organ Class	Adverse Reaction
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
Endocrine Disorders	Diabetes
Gastrointestinal Disorders	Intestinal perforation; Non-infectious peritonitis; Glossitis; Nausea; Pancreatitis
General Disorders and Administration Site Conditions	Pyrexia; Chills; Malaise; Fatigue; Anaphylactic reactions
Hepatobiliary Disorders	Hepatic failure
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
Musculoskeletal, Connective Tissue and Bone Disorders	Osteonecrosis
Nervous System Disorders	CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness; Paresthesia
Ophthalmologic Disorders	Transient blindness/vision loss
Pregnancy, Puerperium and Perinatal Conditions	Fetal death, Abortion
Renal and Urinary Disorders	Proteinuria
Reproductive System and Breast Disorders	Urogenital dysfunction
Respiratory, Thoracic and Mediastinal Disorders	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough; Plural effusion

System Organ Class	Adverse Reaction
Skin and Subcutaneous Tissue Disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS); Dermatitis; Petechiae

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
The use of nitrous oxide anesthesia with methotrexate is contraindicated (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Renal; and 9.4 Drug-Drug Interactions)

9.2 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.

9.3 Drug-Behaviour Interactions

Use of alcohol with pms-METHOTREXATE is contraindicated (see 2 CONTRAINDICATIONS). The effects of smoking on the pharmacokinetics of methotrexate have not been specifically studied.

9.4 Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Amiodarone	C	Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions.	Caution is warranted and therapeutic concentration monitoring is recommended
L-asparaginase	C	The administration of L-asparaginase has been reported	Use with caution.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		to antagonize the effect of methotrexate.	
Ciprofloxacin	T	Renal tubular transport is diminished by ciprofloxacin	Use of pms-METHOTREXATE with this drug should be carefully monitored.
Cytarabine and other cytotoxic agents	C	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 7 WARNINGS AND PRECAUTIONS, Neurologic). Combined use of methotrexate with other cytotoxic agents has not been studied and may increase the incidence of adverse effects.	Use with caution.
Disease Modifying Antirheumatic drugs (DMARDs)	T	Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, or sulfasalazine has not been studied and may increase the incidence of adverse effects.	Use with caution.
Diuretics	C	Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.	Use with caution.
Drugs Highly Bound to Plasma Proteins (e.g., as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides,	T	Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs.	Use with caution.

Proper/Common name	Source of Evidence	Effect	Clinical comment
some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.			
Hepatoxins	C	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.	Patients receiving concomitant therapy with pms-METHOTREXATE and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.
Leflunomide	T	Methotrexate in combination with leflunomide may increase the risk of pancytopenia.	
Mercaptopurine	T	Methotrexate increases the plasma levels of mercaptopurine.	Combination of pms-METHOTREXATE and mercaptopurine may therefore require dose adjustment.
Nephrotoxic Drugs (e.g., aminoglycosides, Amphotericin B, and Cyclosporin)	T	Although not documented, other nephrotoxic drugs could theoretically increase methotrexate toxicity by decreasing its elimination.	Use with caution.
Nitrous Oxide	C	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	In case of accidental coadministration, this effect can be reduced by the use of leucovorin rescue.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		methotrexate) and nephritis (see 2 CONTRAINDICATIONS; and 7 WARNINGS AND PRECAUTIONS, Renal).	
Non-steroidal Anti-inflammatory Drugs (NSAIDs)	C, CT	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.	NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of pms-METHOTREXATE. In treating rheumatoid arthritis with pms-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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral Antibiotics (e.g., tetracycline, chloramphenicol, and nonabsorbable broad-spectrum antibiotics)	C, T	Oral 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.	Use with caution.
Packed Red Blood Cells	C, CT	Patients receiving 24-hr methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged high serum-methotrexate concentrations.	Care should be exercised whenever packed red blood cells and methotrexate are given concurrently.
Penicillins and Sulfonamides	C, CT	Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity have been observed in combination with pms-METHOTREXATE.	Use of methotrexate with penicillins should be carefully monitored.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Probenecid	T	Renal tubular transport is diminished by probenecid	Use of pms-METHOTREXATE with this drug should be carefully monitored.
Proton Pump Inhibitors	C. CT	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.	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.
Psoralen Plus Ultraviolet Light (PUVA) Therapy	C	Skin cancer has been reported in patients with psoriasis or mycosis fungoides (a cutaneous Tcell lymphoma) receiving a concomitant treatment with methotrexate plus PUVA therapy.	
Radiotherapy	C	Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.	
Theophylline	T	Methotrexate may decrease the clearance of theophylline.	Theophylline levels should be monitored when used concurrently with pms-METHOTREXATE.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Vitamins	T	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-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 toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes. Folate deficiency states may increase methotrexate toxicity.	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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of methotrexate have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Methotrexate has immunosuppressive and/or anti-inflammatory effects. The pharmacodynamics of methotrexate show large interpatient variability regardless of the route of administration or disease being treated.

10.3 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.

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.

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.

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 or parenterally.

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 or parenterally. High cerebrospinal fluid concentrations of the drug may be attained by intrathecal administration.

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.

Elimination

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 or parenterally.

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.

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.

Special Populations and Conditions

- **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.

- **Pregnancy and Breast-feeding**
  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.

- **Hepatic Insufficiency**
  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.

- **Renal Insufficiency**
  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.

11 STORAGE, STABILITY AND DISPOSAL

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

Store pms-METHOTREXATE tablets between 15°C and 30°C. Store it away from heat and direct light.

12 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

- 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.
- Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal

- Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.
- Tablets: Place container and tablets in a plastic bag, seal and mark as hazardous waste. Incinerate at 1000°C or higher.

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 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

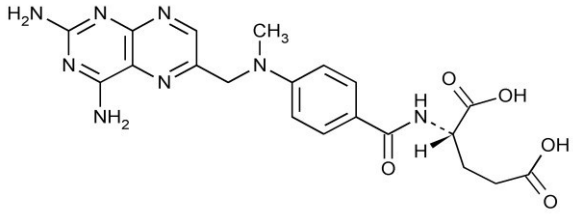
Drug Substance:

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 is a mixture of 4-amino-10methylfolic 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 parenteral 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.

14 CLINICAL TRIALS

The clinical trial data on which the original indications were authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 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.

Carcinogenicity: 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.

Special Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-METHOTREXATE
Methotrexate Tablets USP

Read this carefully before you start taking **pms-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 **pms-METHOTREXATE.**

Serious Warnings and Precautions

- pms-METHOTREXATE should be prescribed by a healthcare professional who is experienced with the use of methotrexate.
- pms-METHOTREXATE can cause serious side effects which may result in death.

Pregnancy:
- pms-METHOTREXATE can cause birth defects or death of an unborn baby when used in pregnant women.
- Female patients who are able to get pregnant:
  - A pregnancy test should be done before you start pms-METHOTREXATE to show that you are not pregnant.
  - If you have psoriasis or rheumatoid arthritis and are pregnant, do not take pms-METHOTREXATE.
  - If you have cancer and you are pregnant or planning to get pregnant: Before starting pms-METHOTREXATE, talk to your healthcare professional about whether the benefits to you outweigh the risks to your baby.
  - Avoid getting pregnant while taking pms-METHOTREXATE and for at least 3 months to 1 year after your treatment.
  - Tell your healthcare professional right away if you think you have become pregnant while taking pms-METHOTREXATE.
- Male patients:
  - Do not father a child while you are taking pms-METHOTREXATE and for at least 3 months to 1 year after your treatment.
  - Tell your healthcare professional right away if you think your partner has become pregnant while you are taking pms-METHOTREXATE.

What is pms-METHOTREXATE used for?
pms-METHOTREXATE is used to treat certain types of cancers, severe psoriasis, psoriatic arthritis, and severe rheumatoid arthritis.

How does pms-METHOTREXATE work?
pms-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, pms-METHOTREXATE acts on the inflammatory cells that cause joint swelling. pms-METHOTREXATE therapy is used to control psoriasis and rheumatoid arthritis, but it will not cure them. In cancer, pms-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.

What are the ingredients in pms-METHOTREXATE?
Medicinal ingredients: Methotrexate disodium
Non-medicinal ingredients: Corn starch, lactose, magnesium stearate, sodium hydroxide and purified water

pms-METHOTREXATE comes in the following dosage forms:
Tablet: 2.5 mg methotrexate (as methotrexate disodium)

Do not use pms-METHOTREXATE if:
- you are allergic to methotrexate, any of the non-medicinal ingredients including lactose, or any component of the container.
- you have severe kidney problems or are on dialysis.
- you are pregnant or plan to become pregnant and have psoriasis or rheumatoid arthritis. If you have cancer and are pregnant or planning a pregnancy, talk to your healthcare professional about whether the benefits to you outweigh the risks to your baby.
- you are breast-feeding.
- you have psoriasis or rheumatoid arthritis and the following:
    - alcoholism (drink excessive alcohol)
    - have chronic liver disease
    - have immune system problems
    - blood or bone marrow problems
- you are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-METHOTREXATE. Talk about any health conditions or problems you may have, including if you:
- Both male and female patients must use effective birth control methods all the time while taking pms-METHOTREXATE and for a few months after the last dose of the drug.
- have peptic ulcer disease or ulcerative colitis
- have a problem with your bone marrow
- have mild or moderate kidney problems
- have or have had liver problems, including if you have or have had hepatitis B or hepatitis C infection and fatty changes or inflammation in your liver
- have an active infection

- have previously had radiation to your head or spine
- drink alcohol
- are taking non-steroidal anti-inflammatory drugs, cytarabine or medicines to treat stomach acid called proton pump inhibitors (like omeprazole, esomeprazole or pantoprazole)
- are also receiving or have received radiation therapy
- are experiencing weakness (debility)
- are over 65 years of age. This is because side effects and medication errors may be more likely in these patients.

Other warnings you should know about:

- **Liver problems**: Taking pms-METHOTREXATE may cause liver problems, which could be fatal. If you have rheumatoid arthritis and regularly drink a lot of alcohol or have psoriasis, your healthcare professional may do a biopsy of your liver before you start treatment. They may repeat it regularly throughout your treatment to see how the medication is affecting your liver.

- Do not drink alcohol.

- **Vaccination:** Talk to your healthcare professional if you need a vaccination. Live vaccines may cause severe infections. Avoid getting a live vaccine or coming in to contact with anyone who has had a live vaccination. Your ability to fight an infection is decreased while taking pms-METHOTREXATE.

- **Sensitivity to sunlight:** pms-METHOTREXATE increases sensitivity to sunlight. Avoid sun exposure and do not use a sunlamp while taking this drug.

- **Pulmonary alveolar hemorrhage**: Methotrexate can cause sudden bleeding in the lungs. This is called **Pulmonary alveolar hemorrhage**. If you suddenly spit or cough up blood, go to the hospital right away. You will need emergency care. This side effect may happen in patients who have other health problems like rheumatic disorder (such as pain in your joints) or vasculitis (such as swelling in an artery or vein).

- **Fertility**:
  - **Females:** pms-METHOTREXATE can cause abnormal periods and other vaginal bleeding problems for a short time during and after treatment. It can also affect your eggs. These conditions may make it harder for you to get pregnant.
  - **Males:** pms-METHOTREXATE can lower sperm count during and after treatment. This may affect your ability to father a child.

  If you are concerned about the possible impact to your fertilty, talk to your your healthcare professional before taking pms-METHOTREXATE.

- **Driving and using machines:** pms- METHOTREXATE can cause fatigue and dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to pms- METHOTREXATE.

- **Monitoring**: Before you start to take pms-METHOTREXATE, your healthcare professional will do blood tests and a chest x-ray. Blood tests will be repeated about once per month. As you are starting your treatment or if your dose of pms-METHOTREXATE changes, your healthcare professional may repeat these tests more often. The blood tests will measure your blood counts and check how your liver and kidneys are working. You may also need to have other tests to measure how your lungs are working.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take pms-METHOTREXATE if you are going to receive a general anesthetic called nitrous oxide (laughing gas).

The following may interact with pms-METHOTREXATE:

- medicines to reduce pain, fever or inflammation called non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (ASA), phenylbutazone
- certain Disease Modifying Antirheumatic drugs (DMARDs) including gold (taken by mouth or injection), penicillamine, hydroxychloroquine, sulfasalazine, leflunomide, or azathioprine
- medicines used to treat acne called retinoids
- a medicine to suppress the immune system called cyclosporin
- a medicine used to treat seizures called phenytoin
- a medicine used to treat gout called probenecid
- medicines used to treat bacterial and fungal infections including amphotericine B, penicillins, tetracycline, vancomycin, nystatin, neomycin, polymyxin B, kanamycin, trimethoprim/sulfamethoxazole, ciprofloxacin, pristinamycin, chloramphenicol
- a medicine used to treat asthma called theophylline
- the vitamin folic acid or vitamin preparations that contain folic acid
- medicines used to treat cancer including chemotherapy, cytarabine, mercaptopurine, L-asparaginase, folinic acid and radiation therapy
- medicines used to treat acid related stomach problems called proton pump inhibitors (PPIs) including omeprazole, esomeprazole, and pantoprazole
- a medicine to treat parasites called pyrimethamine
- a medicine used to treat irregular heartbeat called amiodarone
- medicines used to treat diabetes called sulfonylureas, aminobenzoic acid, sulfonamides, also known as “sulfa drugs”
- packed red blood cells, used for blood transfusions
- Psoralen Plus Ultraviolet Light (PUVA) therapy, which is used to treat skin conditions
- the medicine Triamterene, which is a diuretic or “water pill”

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

How to take pms-METHOTREXATE:

- Always take pms-METHOTREXATE exactly as directed by your healthcare professional. Check with them if you are unsure.
- Swallow tablet whole.
- Your healthcare professional will tell you how often to take pms-METHOTREXATE. How often you take it will depend on why you are taking this medicine.
- **For rheumatoid arthritis or psoriasis:** Take pms-METHOTREXATE **once per week**. It should never be taken every day of the week. However, in some cases, your healthcare professional may instruct you to take pms-METHOTREXATE every 12 hours for 3 doses.
- **For cancer:** how often you take pms-METHOTREXATE depends on the type of cancer you have.
- Do not take more or less pms-METHOTREXATE, and do not take it more often than your healthcare professional has told you.
- The exact amount of medicine you need has been carefully worked out. Taking too much may increase the chance of side effects and may lead to hospitalization or death. Taking too little may not improve your condition.
- If you are taking pms-METHOTREXATE once per week, pick a day of the week when you are most likely to remember to take it. Take your dose on the 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.
- pms-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 healthcare professional to help you plan a way to remember to take your medicines at the right times.
- While you are using pms-METHOTREXATE, your healthcare professional 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 help to prevent kidney problems and keep your kidneys working well.
- Wear gloves when handling pms-METHOTREXATE.

Usual dose:

The dose of pms-METHOTREXATE will be different for different patients. The dose you receive will depend on:

- why you are taking this medicine
- your weight and height
- if you are also taking other medicines.

Your healthcare professional may lower your dose if you have side effects including problems with your liver or kidneys.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-METHOTREXATE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Always take your labelled medicine with you, even if it is empty.

Missed Dose:
If you missed a scheduled dose, contact your healthcare professional for instruction.

If you vomit shortly after taking a dose of pms-METHOTREXATE, check with your healthcare professional. They will tell you whether to take the dose again or to wait until the next scheduled dose.

What are possible side effects from using pms-METHOTREXATE?
These are not all the possible side effects you may have when taking pms-METHOTREXATE. If you experience any side effects not listed here, tell your healthcare professional.

Along with their needed effects, medicines like pms-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 healthcare professional.

- Upset stomach, stomach pain, vomiting, nausea, loss of appetite, dizziness, chills and fever, diarrhea, 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)
- Headaches, hair loss, mood changes, confusion, ringing in the ears, sore eyes, skin rashes, increased sensitivity to sunlight, unexplained weight loss
- Blurred vision, short-term blindness
- Drowsiness, weakness
- Hoarseness
- Pin-point red spots on the skin
- Reddening or whitening of the skin, acne, boils
- Impotence or loss of interest in sex
- Diabetes, thinning of the bones, painful muscles and joints
- Low blood pressure
- Gastrointestinal ulcers

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

pms-METHOTREXATE can cause abnormal test results. Your healthcare professional 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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Nausea and vomiting		✓	
COMMON			
Gastrointestinal Problems: diarrhea, dehydration, abdominal pain, tenderness, chills, fever, extreme thirst, mouth ulcers or inflammation, colitis (inflammation of the colon), difficulty passing urine or stool			✓
Infections: sore throat, fever, chills, or swelling of glands		✓	
Inflammation of the lungs and lung damage: persistent dry cough, shortness of breath, fever		✓	
Myelosuppression (decreased blood cell counts) including: **Anemia** (low red blood cells): tiredness, loss of energy, looking pale, shortness of breath, weakness **Leukopenia** (low white blood cell count): infections, fatigue, fever, aches, pains and flu-like symptoms **Thrombocytopenia** (low platelet count): bruising, more bleeding than usual after an injury, fatigue, weakness		✓ ✓	✓
LESS COMMON			
Lung problems: chest pain, cough, shortness of breath or fever			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Severe headaches			✓
RARE			
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			✓
Urinary tract infection: pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine		✓	
Liver problems: yellowing of the whites of the eyes or skin (jaundice), nausea, tiredness, loss of appetite, fever, skin rash, joint pain and inflammation, pain in the upper right abdomen, pale stools and dark-coloured urine			✓
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, pain or difficulty urinating, lower back or side pain, dark urine			✓
Convulsions: seizure, spasms, shaking or fits			✓
Lymphoma (cancer of the lymph glands): painless swelling of lymph node, swollen tonsils, fever, chills, night sweats, feeling tired, itching, unexplained weight loss, loss of appetite, persistent coughing/ difficulty breathing or not being able to breathe, and headache		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Heart damage: fast heartbeat, palpitations, chest pain, difficulty breathing, fainting			✓
Gastrointestinal bleeding: bloody vomit, black tarry stool			✓
UNKNOWN			
Central Nervous System problems: behaviour changes, decreased consciousness, headache, weakness, numbness, vision loss or double vision, seizures, vomiting, loss of memory			✓
Drug reaction with eosinophilia and systemic symptoms (DRESS; allergic reactions): fever, rash, hives, swelling of eyes, lips or tongue			✓
Pulmonary alveolar haemorrhage: suddenly spit or cough up blood			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

- Store pms-METHOTREXATE at 15°C to 30°C and away from heat and direct light.
- Do not keep outdated medicine or medicine you no longer need.
- Keep out of reach and sight of children.

If you want more information about pms-METHOTREXATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.pharmascience.com), or by calling 1-888-550-6060

This leaflet was prepared by Pharmascience Inc.

Last revised: JAN 08, 2025