

PRODUCT MONOGRAPH

PrMETHOTREXATE SUBCUTANEOUS

Methotrexate Injection BP

50 mg / mL methotrexate (as methotrexate sodium)

Single-Use Pre-Filled
Syringes

Sterile

THERAPEUTIC CLASSIFICATION

Immunosuppressant

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Subcutaneous	50 mg / mL single-use pre-filled syringes	Sodium Chloride, Sodium Hydroxide and Water for injection

INDICATIONS AND CLINICAL USE

METHOTREXATE SUBCUTANEOUS (methotrexate injection) 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)

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

Geriatrics:

The clinical pharmacology of 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:

Safety and effectiveness in pediatric patients have not been established.

Limitation of Use

METHOTREXATE SUBCUTANEOUS is not indicated for the treatment of neoplastic diseases

CONTRAINDICATIONS

METHOTREXATE SUBCUTANEOUS (methotrexate injection) 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 the **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**)
- Pregnancy: Methotrexate can cause fetal death, embryotoxicity, abortion or teratogenic effects when administered to a pregnant woman.
- Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate (see **WARNINGS AND PRECAUTIONS**).
- Breast-feeding mothers: Due to the potential for serious adverse reactions in breast fed infants.
- Patients with alcoholism, alcoholic liver disease or other chronic liver disease.
- Patients with overt or laboratory evidence of immunodeficiency syndromes.
- Patients with 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

- METHOTREXATE SUBCUTANEOUS (methotrexate injection) should be prescribed only by physicians whose knowledge and experience includes the use of immunosuppressant 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 **Special Populations: Pregnant Women** section below). Therefore, use is contraindicated for women of childbearing potential until pregnancy is excluded and pregnant patients (see **CONTRAINDICATIONS**).
- METHOTREXATE SUBCUTANEOUS must be administered **only once a week**. Dosage errors in the use of METHOTREXATE SUBCUTANEOUS (methotrexate injection) can result in serious adverse reactions, including death.

General

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported. It should be emphasized to the patient that the recommended dose is taken weekly.

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

METHOTREXATE SUBCUTANEOUS has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on METHOTREXATE SUBCUTANEOUS 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 METHOTREXATE SUBCUTANEOUS 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 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.

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

Carcinogenesis and Mutagenesis

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 tumors in rheumatoid arthritis. Benefit should be weighed against this potential risk before using methotrexate alone or in combination with other drugs, especially in children or young adults.

Also, see **TOXICOLOGY**.

Gastrointestinal

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

Unexpectedly severe (sometimes fatal) gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some non-

steroidal anti-inflammatory drugs (NSAIDs) (see DRUG INTERACTIONS).

Drug Interactions with Proton Pump Inhibitors (PPI): 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

METHOTREXATE SUBCUTANEOUS should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy.

METHOTREXATE SUBCUTANEOUS may produce marked bone marrow depression with resultant anemia, aplastic anemia, pancytopenia, leucopenia neutropenia and / or thrombocytopenia. In patients with malignancy and pre-existing hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC <3000 / mm³) was seen in 2 patients, thrombocytopenia (platelets <1,000,000 / mm³) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, METHOTREXATE SUBCUTANEOUS should be stopped immediately if there is a significant drop in blood counts. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

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

Hepatic / Biliary / Pancreatic

METHOTREXATE SUBCUTANEOUS has the potential for acute and chronic hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after methotrexate administration and are usually not a reason for modification of METHOTREXATE SUBCUTANEOUS 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 methotrexate, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection. 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 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 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 (Roanigk grades I, II, IIIa), METHOTREXATE SUBCUTANEOUS may be continued and the patient monitored according to the recommendations listed above. METHOTREXATE SUBCUTANEOUS 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 (Roanigk 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

METHOTREXATE SUBCUTANEOUS should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of

immunodeficiency syndromes.

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

Neurologic

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

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

Renal

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. 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. Pulmonary symptoms (especially a dry non-productive 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.

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.

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

Sexual Health

Fertility:

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

Reproduction:

Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with both male and female patients of childbearing potential. The absence of pregnancy must be confirmed before METHOTREXATE SUBCUTANEOUS is used. If women of a sexually mature age are treated, effective contraception must be performed during treatment and from at least six months to one year (see WARNINGS AND PRECAUTIONS - Special Populations – Contraception in females).

Methotrexate is contraindicated during pregnancy in non-oncological indications. If pregnancy occurs during treatment with methotrexate and from six months to one year after, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal fetal development.

In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester. Methotrexate has been shown to be teratogenic to humans; it has been reported to cause fetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related). Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy. The risk of effects on reproduction should be discussed with both male and female patients taking METHOTREXATE SUBCUTANEOUS.

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 methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with 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:

METHOTREXATE SUBCUTANEOUS is contraindicated in pregnant patients (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). METHOTREXATE SUBCUTANEOUS can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. The risk of effects on reproduction should be discussed with both male and female patients taking METHOTREXATE SUBCUTANEOUS.

Women of childbearing potential should not be started on METHOTREXATE SUBCUTANEOUS until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment. Effective contraception must be used during treatment with methotrexate and at least from 6 months to one year after. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning. Pregnancy should be avoided if either partner is receiving METHOTREXATE SUBCUTANEOUS.

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. There are insufficient data to estimate the risks of malformations or miscarriage following paternal exposure. As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and from 6 months to one year after cessation of methotrexate. Men should not donate semen during therapy or from 6 months to one year following discontinuation of methotrexate.

Breast-feeding:

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, METHOTREXATE SUBCUTANEOUS is contraindicated in breast-feeding mothers.

Pediatrics:

Safety and effectiveness in pediatric patients have not been established.

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 should be considered, and these patients should be closely monitored for early signs of toxicity.

Renal Impairment: METHOTREXATE SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION-Special populations**).

Monitoring and Laboratory Tests

General:

Patients undergoing methotrexate therapy should be informed of the early signs and symptoms

of toxicity and closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count (CBC) with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, and hepatic enzyme levels and renal function every 1 to 2 months.

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.

Liver:

Liver biopsies prior to METHOTREXATE SUBCUTANEOUS therapy are not indicated routinely. Liver function tests (LFTs) should be determined prior to the initiation of therapy with METHOTREXATE SUBCUTANEOUS and they should be monitored regularly throughout therapy. A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of 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.

Respiratory:

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

Serum Level Monitoring:

Serum methotrexate level monitoring can significantly reduce methotrexate toxicity and mortality.

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

Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate 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).

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 in **WARNINGS AND PRECAUTIONS**. That section should also be consulted when looking for information about

adverse reactions with methotrexate.

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.

Adverse Drug Reactions by Organ System

Blood and lymphatic system disorders

Leukopenia, anaemia, thrombopenia, pancytopenia, agranulocytosis and severe courses of bone marrow depression, lymphoproliferative disorders.

Cardiac disorders

Pericarditis, pericardial effusion and pericardial tamponade.

Eye disorders

Visual disturbances and retinopathy.

Gastrointestinal disorders

Stomatitis, dyspepsia, nausea, loss of appetite, oral ulcers, diarrhoea, pharyngitis, enteritis, vomiting, gastrointestinal ulcers, haematemesis, haemorrhage and toxic megacolon.

General disorders and administration site conditions

Allergic reactions, anaphylactic shock, allergic vasculitis, fever, conjunctivitis, infection, sepsis, wound-healing impairment, hypogammaglobulinaemia and local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.

Hepatobiliary disorders

Elevated transaminases, cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin, acute hepatitis and hepatic failure.

Metabolism and nutrition disorders

Precipitation of diabetes mellitus.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia and osteoporosis, osteonecrosis of jaw (secondary to lymphoproliferative disorders).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

Nervous system disorders

Headache, tiredness, drowsiness, dizziness, confusion, depression, impaired vision, pain, muscular asthenia or paraesthesia/hypoesthesia, changes in sense of taste (metallic taste), convulsions, meningism, paralysis and leukoencephalopathy.

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

Inflammation and ulceration of the vagina, loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation and vaginal discharge.

Respiratory, thoracic and mediastinal disorders

Pneumonia, interstitial alveolitis / pneumonitis often associated with eosinophilia, symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever, pulmonary fibrosis, *Pneumocystis carinii* pneumonia, shortness of breath and bronchial asthma, pleural effusion, epistaxis, and pulmonary alveolar haemorrhage.

Skin and subcutaneous tissue disorders

Exanthema, erythema, pruritus, photosensitisation, loss of hair, increase in rheumatic nodules, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticarial, increased pigmentation, acne, ecchymosis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis and telangiectasia.

Vascular disorders

Hypotension and thromboembolic events.

Other Adverse Drug Reactions

Adverse Reactions Reported in Rheumatoid Arthritis

Incidence greater than 10%: elevated liver enzymes 15%, nausea / vomiting 10%.

Incidence 3% to 10%: stomatitis, thrombocytopenia.

Incidence 1% to 3%: rash / pruritus / dermatitis, alopecia, diarrhea, dizziness, leucopenia and pancytopenia.

Adverse Reactions in Psoriasis

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

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal hematologic and clinical chemistry findings are discussed in **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests.**

Post-marketing 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; <i>Pneumocystis carinii</i> pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; <i>H. simplex</i> hepatitis; Disseminated <i>H. simplex</i> ; 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; Injection site necrosis
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; Swelling/edema at sites independent of injection
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

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

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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 METHOTREXATE SUBCUTANEOUS. 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.

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.

Packed Red Blood Cells

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

Ciprofloxacin

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

Radiotherapy

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

Mercaptopurine

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

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 sulfonyleureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.

Probenecid

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

Nephrotoxic Drugs

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

Penicillins and Sulfonamides

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

Oral Antibiotics

Oral antibiotics such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of METHOTREXATE SUBCUTANEOUS 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.

Theophylline

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

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered METHOTREXATE SUBCUTANEOUS.

In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes.

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

Folate deficiency states may increase methotrexate toxicity.

Hepatotoxins

The potential for increased hepatotoxicity when METHOTREXATE SUBCUTANEOUS is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with METHOTREXATE SUBCUTANEOUS and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Proton Pump Inhibitors (PPI)

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.

Amiodarone

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

Diuretics

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

Psoralen Plus Ultraviolet Light (PUVA) Therapy

Skin cancer has been reported in few patients with psoriasis receiving a concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).

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 co-administration, this effect can be reduced by the use of leucovorin rescue.

Drug-Food Interactions

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

Drug-Lifestyle Interactions

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

Methotrexate may cause adverse reactions such as dizziness and fatigue which can affect the ability to drive or operate machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

Recommended Dose and Dosage Adjustments

Psoriasis

Recommended Starting Dose Schedules

- Weekly single, SC dose schedule: 7.5 to 25 mg per week until adequate response is achieved.

The recommended initial dose is 7.5 mg of methotrexate once 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 amount of drug and to the longest possible rest period. The use of METHOTREXATE SUBCUTANEOUS may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis

Recommended Starting Dosage Schedules

- Weekly single, SC dose schedule: 7.5 to 25 mg per week until adequate response is achieved.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; The recommended initial dose is 7.5 mg of methotrexate **once weekly**, Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded.

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, the dose should be reduced gradually to the lowest possible effective maintenance dose.

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 SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS).

Table 5: Dose Adjustments in Patients with Renal Insufficiency

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

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established (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 5 for reduced doses in patients with renal impairment.

Administration

METHOTREXATE SUBCUTANEOUS is injected **once weekly**.

METHOTREXATE SUBCUTANEOUS should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

The administration should routinely be done by health professionals. The treating physician can, in selected cases for whom it is appropriate, delegate the subcutaneous administration to the patient themselves or to a caregiver. In these cases, patients or caregivers must receive proper training on how to prepare and correctly administer METHOTREXATE SUBCUTANEOUS.

At minimum, the first injection of METHOTREXATE SUBCUTANEOUS should be performed under direct medical supervision.

METHOTREXATE SUBCUTANEOUS solution should be yellow-brown in colour and should be clear with no particles in it. Visually inspect METHOTREXATE SUBCUTANEOUS for particulate matter and discoloration prior to administration. Do not use METHOTREXATE SUBCUTANEOUS if the seal is broken.

Missed Dose

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

OVERDOSAGE

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

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

Pharmacokinetics

Absorption:

Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

Distribution:

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 0.8 L / kg (40% to 80% of body weight). Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally.

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. 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. 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.

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis.

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

Special Populations and Conditions

Breast-feeding 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.

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 reach of children.

Store METHOTREXATE SUBCUTANEOUS between 15 to 25°C. Store it away from heat and in the outer carton to protect it from light.

Avoid freezing. Any unused solution should be discarded.

SPECIAL HANDLING INSTRUCTIONS

General:

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

Safe Handling and Disposal:

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 this drug should avoid contact with skin and inhalation of airborne particles. In the event of contamination, the affected

area must be rinsed immediately with ample amounts of water.

Pregnant or breast-feeding healthcare providers or care-givers should not handle and/or administer METHOTREXATE SUBCUTANEOUS.

DOSAGE FORMS, COMPOSITION AND PACKAGING

METHOTREXATE SUBCUTANEOUS (methotrexate injection) 50 mg / mL (as methotrexate sodium) is available in single-use USP type I glass pre-filled syringes. Non-medicinal ingredients include sodium chloride, sodium hydroxide and water for injection.

METHOTREXATE SUBCUTANEOUS is a clear, yellow-brown solution that is free of particles. METHOTREXATE SUBCUTANEOUS is available as follows (in colour-coded packaging with colour- matched syringe finger grips);

- * 1 mL syringe with 0.15 mL solution for injection, equivalent to 7.5 mg methotrexate (grey)
- * 1 mL syringe with 0.2 mL solution for injection, equivalent to 10 mg methotrexate (light green)
- * 1 mL syringe with 0.25 mL solution for injection, equivalent to 12.5 mg methotrexate (light blue)
- * 1 mL syringe with 0.3 mL solution for injection, equivalent to 15 mg methotrexate (purple)
- * 1 mL syringe with 0.35 mL solution for injection, equivalent to 17.5 mg methotrexate (pink)
- * 1 mL syringe with 0.4 mL solution for injection, equivalent to 20 mg methotrexate (red)
- * 1 mL syringe with 0.45 mL solution for injection, equivalent to 22.5 mg methotrexate (dark green)
- * 1 mL syringe with 0.5 mL solution for injection, equivalent to 25 mg methotrexate (dark blue)

All syringes are available in cartons of 1 or 4 single-use USP type I glass pre-filled syringes with embedded injection needles (type 27 G, ½ inch, made from stainless steel).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Methotrexate

Chemical name: Methotrexate

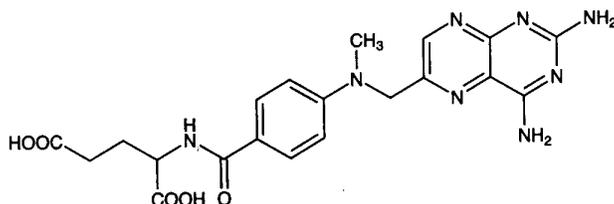
N-[4-[[[(2,4-diamino-6-pteridiny]methylamino]benzoyl]-L- glutamic acid

Amethopterin

4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid 4-Amino-10-methylfolic acid

Molecular formula and molecular mass: C₂₀H₂₂N₈O₅ (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-10-methylfolic acid and closely related compounds and is equivalent to not less than 94.0% of C₂₀H₂₂N₈O₅ 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.

Note: methotrexate sodium is formed in situ during drug product manufacturing.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

Absorption

Methotrexate is generally completely absorbed following parenteral administration, and 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 parenterally.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninfamed 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, and tissues. A small amount of metabolism to 7-hydroxy methotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxy methotrexate 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, or rheumatoid arthritis.

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 delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination.

TOXICOLOGY

The acute toxicity (LD₅₀) of methotrexate in mice ranges from 65 to 70 mg/kg intravenously and 45 to 90 mg / kg intraperitoneally. The acute oral toxicity (LD₅₀) in rats is 317 mg / kg; subcutaneously, it is 58 mg / kg and intraperitoneally it ranges from 80 to 464 mg / kg.

In a 22 month carcinogenicity study in rats that received methotrexate 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 $2 \times 10^{-8} M$. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate resulting in plasma levels in excess of $2 \times 10^{-8} M$ 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 METHOTREXATE SUBCUTANEOUS
Methotrexate Injection BP**

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

ABOUT THIS MEDICATION

What the medication is used for:

METHOTREXATE SUBCUTANEOUS belongs to a group of medicines known as immunosuppressants. It is used to treat psoriasis and rheumatoid arthritis.

What it does:

In rheumatoid arthritis, methotrexate acts on the inflammatory cells that cause joint swelling. METHOTREXATE SUBCUTANEOUS therapy is used to control psoriasis and rheumatoid arthritis but it will not cure them. Some normal cells in the body may be affected as well.

Ask your doctor if you have any questions about why it has been prescribed for you.

When it should not be used:

Do not take METHOTREXATE SUBCUTANEOUS if you:

- Are allergic to methotrexate or any component of the drug (see What the nonmedicinal ingredients are).
- Have any blood disorders including:
 - bleeding from a lack of blood cells called platelets.
 - low iron in the blood (anemia).
- Have an immune system disorder such as AIDS (autoimmune deficiency syndrome) or HIV, the virus which causes AIDS.
- Have an infection.
- Have severe kidney problems.
- Have severe liver disorder.
- Suffer from alcoholism or alcoholic liver disease.
- Have a stomach ulcer.
- Have inflammation and bleeding from the rectum, with abdominal pain and diarrhea (ulcerative colitis).
- Are pregnant (see section “Pregnancy and Fertility”).
- Are breastfeeding (see section “Pregnancy and Fertility”).
- You are on dialysis
- You 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 nonmedicinal ingredients are:

Sodium chloride, sodium hydroxide and water for injection.

What dosage forms it comes in:

METHOTREXATE SUBCUTANEOUS (methotrexate injection) 50 mg / mL (as methotrexate sodium) is available in single-use pre-filled syringes.

METHOTREXATE SUBCUTANEOUS is available in 8 doses that are colour-coded as follows:

Pre-filled syringe	Colour- code
1 mL syringe with 0.15 mL solution for injection, equivalent to 7.5 mg methotrexate	Grey
1 mL syringe with 0.2 mL solution for injection, equivalent to 10 mg methotrexate	Light green
1 mL syringe with 0.25 mL solution for injection, equivalent to 12.5 mg methotrexate	Light blue
1 mL syringe with 0.3 mL solution for injection, equivalent to 15 mg methotrexate	Purple
1 mL syringe with 0.35 mL solution for injection, equivalent to 17.5 mg methotrexate	Pink
1 mL syringe with 0.4 mL solution for injection, equivalent to 20 mg methotrexate	Dark red
1 mL syringe with 0.45 mL solution for injection, equivalent to 22.5 mg methotrexate	Dark green
1 mL syringe with 0.5 mL solution for injection, equivalent to 25 mg methotrexate	Dark blue

All syringes are available in cartons of 1 or 4 USP type I glass pre-filled syringes with single-use pre-filled syringes with embedded injection needles. The carton and finger grip on the syringe are colour coded to match.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

METHOTREXATE SUBCUTANEOUS should be prescribed by a doctor who is experienced with the use of methotrexate therapy.

- You should not plan to have children while taking METHOTREXATE SUBCUTANEOUS or for a while after stopping treatment. (Talk to your doctor for further details). Use a reliable method of birth control to prevent pregnancy.
- METHOTREXATE SUBCUTANEOUS **must only be taken once a week**. Dosage errors of METHOTREXATE SUBCUTANEOUS can cause serious toxic reactions which may result in death.

Before Using This Medicine

IMPORTANT PLEASE READ

Before you begin treatment with METHOTREXATE SUBCUTANEOUS, you should talk to your doctor about the good this medicine will do as well as the risks of using it.

You and your doctor should decide together if you will take METHOTREXATE SUBCUTANEOUS. In deciding to use a medicine, the following should be considered:

Allergies:

- Tell your doctor if you have ever had any unusual or allergic reaction to methotrexate.

Pregnancy and Fertility:

- Tell your doctor if you are pregnant or if you plan to have children. Do not use METHOTREXATE SUBCUTANEOUS during pregnancy or if you are trying to become pregnant. Methotrexate can cause birth defects, harm the unborn child or cause miscarriage. It is associated with malformations of the skull, face, heart and blood vessels, brain and limbs. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant.
- In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.
- You must avoid becoming pregnant whilst taking methotrexate from 6 months to one year after treatment is stopped by using reliable contraception throughout this time. If you do become pregnant while taking METHOTREXATE SUBCUTANEOUS or suspect you might be pregnant, speak to your doctor right away. You should be offered advice regarding the risk of harmful effects on the child through treatment.
- If you wish to become pregnant you should consult your doctor, who may refer you for specialist advice before the planned start of treatment.

Methotrexate temporarily affects sperm and egg production.

Male Fertility

- Methotrexate may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or donating semen whilst taking methotrexate and from 6 months to one year after treatment is stopped.

Breast-feeding:

- Stop breast feeding prior to and during treatment with METHOTREXATE SUBCUTANEOUS.

Children:

- METHOTREXATE SUBCUTANEOUS is not for use

in children.

Older adults:

- Side effects may be more likely to occur in the elderly, who are usually more sensitive to the effects of METHOTREXATE SUBCUTANEOUS.

Other medicines:

- When you are taking METHOTREXATE SUBCUTANEOUS, it is important that your doctor know if you are taking any other prescription or non-prescription medicine. They should also be told if you have ever been treated with x-rays or cancer medicines or if you drink alcohol.

Other medical problems:

The presence of other medical problems may affect the use of METHOTREXATE SUBCUTANEOUS. Tell your doctor if you have any other medical problems, especially:

- Alcohol abuse (or history of)
- Chickenpox (including recent exposure) or Herpes zoster (shingles)
- Colitis
- Disease of the immune system
- Gout (or history of)
- Kidney stones (or history of)
- Infection
- Intestine blockage
- Kidney disease
- If you are dehydrated or have a lot of vomiting, diarrhea, or sweating.
- Liver disease, including hepatitis B and C infection
- Mouth sores or inflammation
- Stomach ulcer

Precautions while using this medicine

It is very important that your doctor check your progress at regular visits to make sure that this medicine is working properly and to check for unwanted effects.

Do not drink alcohol while taking METHOTREXATE SUBCUTANEOUS. Alcohol can increase the chance of liver problems.

Some patients who take METHOTREXATE SUBCUTANEOUS may become more sensitive to sunlight than they are normally. Avoid too much sun exposure and do not use a sunlamp until you see how you react to the sun, especially if you tend to burn easily.

You should not receive certain vaccinations while taking METHOTREXATE SUBCUTANEOUS. Discuss this with your doctor. Avoid anyone who has had oral polio vaccine for at least six weeks. Do not get close to them or stay in the same room for very long. If this is not possible, wear a mask over your nose and mouth.

IMPORTANT PLEASE READ

Some side effects such as dizziness and fatigue may affect the ability to drive or operate machinery. These activities should be avoided. If you have any concerns, please consult your doctor.

METHOTREXATE SUBCUTANEOUS can lower the number of white blood cells in your blood temporarily, increasing the chance of getting an infection. It can also lower the number of platelets, which are necessary for proper blood clotting. If this happens, there are certain precautions you can take, especially when your blood count is low to reduce the risk of infection or bleeding:

- If you can, avoid people with infections. Check with your doctor immediately if you think you are getting an infection or if you get a fever or chills, cough or hoarseness, lower back or side pain, or painful or difficult urination.
- Check with your doctor immediately if you notice any unusual bleeding or bruising; black, tarry stools; blood in urine or stools; or pinpoint red spots on your skin.
- Be careful when using a regular toothbrush, dental floss, or toothpick. Check with your doctor before having any dental work done.
- Do not touch your eyes or the inside of your nose unless you have just washed your hands.
- Be careful not to cut yourself when you are using sharp objects such as scissors or a razor.
- Avoid contact sports or other situations where bruising or injury could occur.

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

Do not take METHOTREXATE SUBCUTANEOUS 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

Tell your doctor and pharmacist what prescription and non-prescription medications you are taking. METHOTREXATE SUBCUTANEOUS may interact with other medicines such as:

- acetyl salicylic acid (ASA) and other pain killers or nonsteroidal anti-inflammatory drugs (NSAIDs)

- Disease Modifying Antirheumatic drugs (DMARDs), such as gold, penicillamine, hydroxychloroquine, or sulfasalazine
- some antibiotics (including ciprofloxacin, penicillins, tetracycline, chloramphenicol, pristinamycin, vancomycin, neomycin, kanamycin, nystatin, polymyxin B, trimethoprim/sulfamethoxazole and sulfonamides, and medicines to prevent malaria – pyrimethamine)
- some epilepsy treatments
- some cancer treatments
- some vaccines
- some medicines used to lower your cholesterol (including cholestyramine)
- azathioprine (used to prevent transplant organ rejection)
- cytarabine (used to treat leukemia)
- leflunomide (used to treat rheumatoid arthritis)
- mercaptopurine (used to treat leukemia)
- nitrous oxide anaesthesia
- probenecid (used to treat gout)
- retinoid medicines (used to treat acne)
- sulfonylureas (used to treat diabetes)
- theophylline (used to treat asthma)
- the vitamin folic acid
- phenytoins
- proton pump inhibitors (PPI). They are drugs used to treat acid related stomach problems. Some PPIs are omeprazole, esomeprazole, and pantoprazole.
- amiodarone (used to treat irregular heart beat)
- triamterene (diuretic or “water pill”)
- PUVA therapy (used to treat skin conditions)

It is very important to tell your doctor about all other medicines you are taking including those you buy without a prescription. You may need to receive different amounts of your medicine or you may need to receive different medicines.

Tell any doctor that is treating you that you are taking METHOTREXATE SUBCUTANEOUS.

If you have not told your doctor or pharmacist about any of the above, tell them before you are given METHOTREXATE SUBCUTANEOUS.

PROPER USE OF THIS MEDICATION

Take METHOTREXATE SUBCUTANEOUS 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.

METHOTREXATE SUBCUTANEOUS is injected under

IMPORTANT PLEASE READ

the skin by or under the supervision of a healthcare professional **once a week** only.

At the start of your therapy, METHOTREXATE SUBCUTANEOUS will be injected by your healthcare professional. Your doctor may decide that you are able to learn how to inject METHOTREXATE SUBCUTANEOUS under the skin yourself, and instruct you or your caregiver on how to inject METHOTREXATE SUBCUTANEOUS.

Do not try to inject METHOTREXATE SUBCUTANEOUS until you or your caregiver have received proper training and feel comfortable with the procedure. Ask your healthcare professional any questions you may have. Your first self-injection of METHOTREXATE SUBCUTANEOUS should be performed with your doctor. Always use METHOTREXATE SUBCUTANEOUS exactly as your healthcare professional has shown you. Read the INSTRUCTIONS FOR USE in full every time before you inject METHOTREXATE SUBCUTANEOUS.

Pregnant or breast-feeding healthcare personnel or caregivers should not handle and/or inject METHOTREXATE SUBCUTANEOUS.

Each METHOTREXATE SUBCUTANEOUS syringe can be used only one time. It must be discarded after use in a sharps container (see Figure L).

Contact your doctor if you notice redness, swelling, heat or oozing at the injection site.

While you are using METHOTREXATE SUBCUTANEOUS, 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.

METHOTREXATE SUBCUTANEOUS 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.

INSTRUCTIONS FOR USE FOR SUBCUTANEOUS SELF-INJECTION:

Follow these instructions with all doses of METHOTREXATE SUBCUTANEOUS. Check the packaging to make sure that you have the right syringe that corresponds to the dose your doctor has prescribed for you.

Carefully read the instructions below before injection, and always use the injection technique advised.

IMPORTANT: Methotrexate should not come into contact with the surface of the skin or mucous membranes. If this happens, rinse the area right away with plenty of water.

The parts of the METHOTREXATE SUBCUTANEOUS pre-filled syringe are shown below (see Figure A)

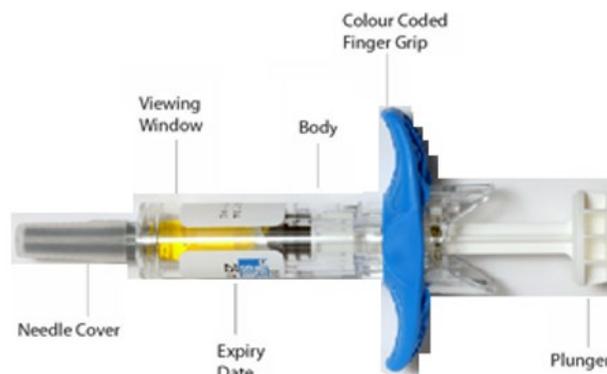
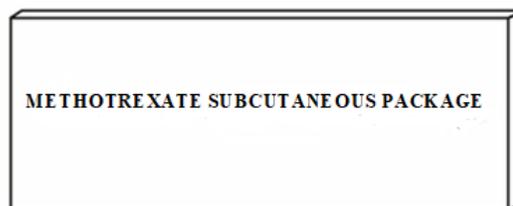


Figure A

Note: The finger grip on your METHOTREXATE SUBCUTANEOUS pre-filled syringe may be a different colour than shown in the Figures in this Instructions for Use. See above section “What dosage forms it comes in:” for more information on colour-coding.

STEP I : PREPARATION

1. Choose a clean, well-lit, flat area to work.
2. Wash your hands well with soap and warm water.
3. Gather the following supplies and place them on the flat work area (see Figure B):
 - 1 package containing a METHOTREXATE SUBCUTANEOUS Pre-Filled Syringe.
 - 1 alcohol pad
 - 1 cotton ball or gauze pad.
 - 1 sharps container for safe disposal of used needles and syringes.



1 package containing a Methotrexate Subcutaneous pre-filled syringe

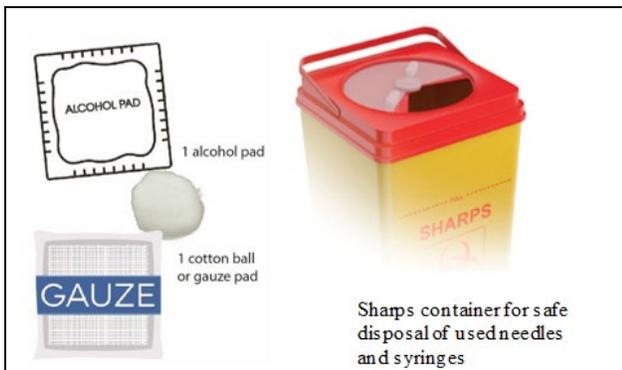


Figure B

Ask your pharmacist about where you can get a sharps container. If you do not have a sharps container, you may use a household container that:

- is made of heavy-duty plastic or metal,
 - can be closed with a tight-fitting, puncture-resistant lid,
 - is upright and stable during use,
 - is leak-resistant, and
 - is properly labelled to warn of hazardous waste. Using a marker, write “BIOHAZARD” on the container.
4. Check the expiry date on the METHOTREXATE SUBCUTANEOUS pre-filled syringe packaging

! Do not use if the expiry date has passed. If expired, discard the syringe in a sharps container (see Step VI, Figure L) and get a new one.

STEP II: INJECTION SITE PREPARATION

1. Choose an injection site (see Figure C). You may inject METHOTREXATE SUBCUTANEOUS into your abdomen or thigh. A caregiver may give you the injection in the back of your upper arm,
 - Abdomen: Maintain a distance of about 5 cm from the belly button (navel). Do not inject above the bottom rib. OR
 - Thigh: Inject into the outer, upper side of your right or left thigh. Maintain a distance of about 5 cm from both your knee and your groin. OR
 - Back of Upper Arm (administration by caregiver only): Give the injection into the back of the upper arm, just below the shoulder.

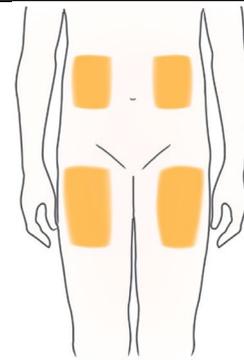


Figure C

! Do not inject METHOTREXATE SUBCUTANEOUS in any other areas of the body.

Choose a different injection site each time you give yourself an injection (e.g. right thigh then left thigh). This may reduce the risk of developing irritation at the injection site.

! Do not inject METHOTREXATE SUBCUTANEOUS where the skin hurts or is hard, tender, bruised, red, scarred or has stretch marks. If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions.

Always inject yourself while sitting or lying down, not standing up.

2. Clean the injection site:

- Wipe the injection site with an alcohol pad (see Figure D).
- Allow the site to dry for at least 60 seconds.
- **Do not** fan or blow on the clean area.
- **Do not** touch this area before injection.



Figure D

STEP III: PREPARE THE SYRINGE AND NEEDLE



Figure E

1. Take the blister tray packaging containing the METHOTREXATE SUBCUTANEOUS syringe out of the carton. Open the METHOTREXATE SUBCUTANEOUS blister packaging:
 - Remove Methotrexate Subcutaneous pre-filled syringe from the packaging at room temperature.
2. Grasp the pre-filled syringe by the body and take it out of the packaging. **Do not** hold or touch the plunger at any time.
3. Check the syringe and the solution
 - Check the syringe for visual defects or cracks.
 - ⚠ **Do not** use the syringe if damaged. If damaged, discard the syringe in a sharps container (see Step VI) and get a new syringe.
 - Look at the solution through the viewing window on the syringe. The solution should be yellow-brown in colour and should be clear with no particles in it.
 - ⚠ **Do not** use the syringe if the solution is discoloured or cloudy, or if it contains visible particles. If discoloured or cloudy, or if it contains visible particles, discard the syringe in a sharps container (see Step VI) and get a new syringe.
 - You may see air bubbles. This is normal. You do not need to remove these. The air bubbles ensure the full and exact dose is delivered.

4. REMOVE THE NEEDLE COVER
 - Holding the syringe by the body in 1 hand, face the needle away from you.
 - **Do not** hold or touch the plunger at any time;
 - Pull the needle cap straight off with your other hand (see Figure F);

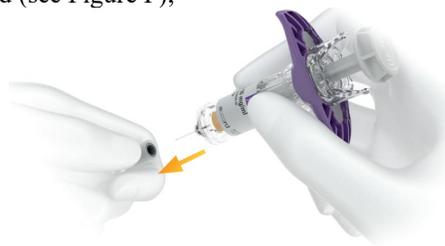


Figure F

- **Do not** touch the needle or allow it to touch any surface.
 - You may see a drop of liquid at the end of the needle. This is normal.
 - Discard the needle cover in a sharps container right away (see Step VI, Figure L).

⚠ **Never** put the needle cover back on after removal. Once the cover is removed, use the syringe immediately.

STEP IV: INJECT METHOTREXATE SUBCUTANEOUS

1. Hold the body of the syringe in 1 hand like a pencil or dart (see Figure G).
2. With the other hand, use your thumb and index finger to grasp and hold a fold of cleaned skin at the injection site. Using a quick and dart-like motion, insert the needle straight into the fold of skin into the injection site on a 90 degree angle. **Do not** hold or push the plunger while inserting the needle into the skin.

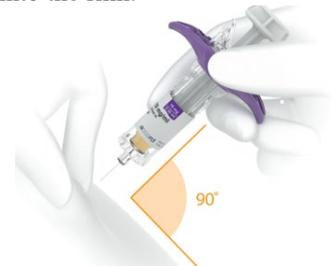


Figure G

3. Insert the needle all the way into the fold of skin. Slowly and steadily press down on the plunger with your thumb and inject all of the liquid under your skin.



Figure H

- Push the plunger all the way down until it stops moving.
- Hold the skin securely until the injection is completed.



Figure I

4. Before you remove the needle, check that the syringe is completely empty. Keep the syringe still and slowly lift your thumb off the plunger rod head;
 - The plunger rod will move up with your thumb and the spring will retract the needle from the site, into the needle safety guard.



Figure J

STEP V: AFTER THE INJECTION

1. Discard the pre-filled syringe directly into the sharps container immediately after use (Step VI)
2. Press a cotton ball or gauze pad on the injection site if you see any blood. Hold it for about 10 seconds (see Figure K). **Do not** rub the injection site because this will irritate the site.



Figure K

STEP VI: DISPOSAL OF USED SUPPLIES

1. Place the used METHOTREXATE SUBCUTANEOUS pre-filled syringe in a sharps container immediately after use (see Figure L).

! Do not recap the needle.

! Do not reuse the syringe. The syringe must be discarded after use.

! Do not throw away the used syringe in household trash.

! Be careful not to touch the needle. If you or someone around you is injured by the needle, contact your healthcare professional right away.

! Always keep the container out of the reach and sight of children.

! Do not throw away the sharps container in your household trash or recycle it. When the container is full, follow your healthcare professional's instructions to dispose of it safely.



Figure L

Place the used alcohol pads, cotton balls, gauze and packaging in your household trash, unless you are instructed otherwise.

Always keep the syringe out of the reach of children.

Usual adult dose:

The dose of METHOTREXATE SUBCUTANEOUS 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. If you have any questions about the proper dose of METHOTREXATE SUBCUTANEOUS, ask your doctor.

The doctor may decrease your dose if you have problems with your kidneys.

Overdose

IMPORTANT PLEASE READ

If you think you have taken too much METHOTREXATE SUBCUTANEOUS, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose

- If you missed a scheduled dose, or have any doubts or concerns about missed doses, contact your doctor for instruction

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

The most common side effects include:

- Upset stomach, stomach pain, vomiting, nausea, loss of appetite, dizziness,
- 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.

Less common side effects are:

- Headaches, hair loss, mood changes, confusion, ringing in the ears, sore eyes, skin rashes.
- 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.

Rarely and generally at higher doses for treatment of other diseases, METHOTREXATE SUBCUTANEOUS 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

More rarely, it can cause:

- Skin rash and other skin disorders.
- Cancer of lymph glands, sudden death.
- Lymphoproliferative disorders (excessive growth of white blood cells)

Although the frequency is unknown, it can cause:

- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Swelling in areas of the body that do not involve the injection sites.
- Reduced senses of touch or temperature, numbness or feelings of prickling (pins and needles)

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 get immediate medical help
		Only if severe	In all cases	
Common	Diarrhea or mouth		√	
	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		√	
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		√	

IMPORTANT PLEASE READ

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 get immediate medical help
	Only if severe	In all cases	
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 Pulmonary alveolar haemorrhage: suddenly spit or cough up blood			√

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

HOW TO STORE IT

- Store METHOTREXATE SUBCUTANEOUS between 15- 25°C. Any unused solution should be discarded.
- Keep out of the reach and sight of children.
- Store it at room temperature and away from heat. Store it in the original carton to protect it from light. Avoid freezing.
- Do not keep outdated medicine or medicine no longer needed. Properly discard of this medicine in a sharps container when it is expired or no longer needed. Talk to your pharmacist if you have any questions.

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.

MORE INFORMATION

If you want more information about METHOTREXATE SUBCUTANEOUS:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); or by calling the sponsor Accord Healthcare Inc. at 1-866-296-0354.

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