

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr METHOTREXATE SUBCUTANEOUS

Methotrexate Injection

Solution, 7.5 mg / 0.15 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 10 mg / 0.2 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 12.5 mg / 0.25 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 15 mg / 0.3 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 17.5 mg / 0.35 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 20 mg / 0.4 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 22.5 mg / 0.45 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

Solution, 25 mg / 0.5 mL (50 mg / mL) methotrexate (as methotrexate sodium), single-use pre-filled syringe for subcutaneous injection

BP

Immunosuppressant

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RECENT MAJOR LABEL CHANGES

7. Warnings and Precautions

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

Limitation of Use

METHOTREXATE SUBCUTANEOUS is not indicated for the treatment of neoplastic diseases.

1.1 Pediatrics

Safety and effectiveness in pediatric patients have not been established.

1.2 Geriatrics

The clinical pharmacology of methotrexate has not been well studied in older individuals (≥ 65 years of age). 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.

2 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 [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#) section.
- In patients with severe renal impairment including end stage renal disease with and without dialysis (see [7 WARNINGS AND PRECAUTIONS- Renal](#) and [7.1 Special Populations](#), and [4 DOSAGE AND ADMINISTRATION](#)).
- 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 [7 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 [7 WARNINGS AND PRECAUTIONS- Renal](#) and [9 DRUG INTERACTIONS- 9.4 Drug-Drug Interactions](#)).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 [7 WARNINGS AND PRECAUTIONS- General](#)).
- Methotrexate has been reported to cause fetal death and/or congenital anomalies (see [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 (see [2 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

METHOTREXATE SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see [2 CONTRAINDICATIONS](#)). Methotrexate is excreted to a significant extent by the kidneys, thus in patients with renal impairment, doses may need to be adjusted to prevent accumulation of drug (see [Recommended Dose and Dosage Adjustments](#) for recommended starting doses in renally impaired patients).

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.

4.2 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 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 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 SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see [2 CONTRAINDICATIONS](#)). 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 provides recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide intersubject pK variability.

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

Hepatic Impairment: METHOTREXATE SUBCUTANEOUS is contraindicated in patients with alcoholic liver disease or other chronic liver disease. Patients with obesity, diabetes, hepatic fibrosis or steatohepatitis are at increased risk for hepatic injury and fibrosis secondary to methotrexate, and should be monitored closely.

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

4.3 Reconstitution

METHOTREXATE SUBCUTANEOUS is available in ready to use pre-filled syringes. No reconstitution is required.

4.4 Administration

METHOTREXATE SUBCUTANEOUS is injected **once weekly**.

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 discolouration prior to administration. Do not use METHOTREXATE SUBCUTANEOUS if the seal is broken.

4.5 Missed Dose

If a scheduled dose is missed, the next dose should be given as soon as possible. However, the total weekly dose should not exceed 25 mg.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous	Solution 50 mg / mL, single-use pre-filled syringes	Sodium chloride, sodium hydroxide, and water for injection

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

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), packed in blisters.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

General

METHOTREXATE SUBCUTANEOUS has the potential for serious toxicity, which can be fatal.

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.

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.

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 [5 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 [16 NON-CLINICAL 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 [9 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 [9 DRUG INTERACTIONS: 9.4 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 [9 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 pre-existing 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 (Roienigk 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 (Roienigk 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.

Methotrexate may cause reactivation of other inactive chronic infections (e.g. herpes zoster, tuberculosis) besides chronic hepatitis B or C (see [Hepatic/Biliary/Pancreatic](#)).

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.

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: e.g., 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).

Neurologic

Encephalopathy/leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications as there are also reports of leukoencephalopathy in patients who received low doses (up to 25 mg/week) of methotrexate therapy for rheumatoid arthritis or psoriatic arthritis.

Discontinuation of METHOTREXATE SUBCUTANEOUS does not always result in complete recovery.

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

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

Renal

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. 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 alkalization 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 DRUG INTERACTIONS- 9.4 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 jirovecii* pneumonia, may occur with

METHOTREXATE SUBCUTANEOUS therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia 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 [7 WARNINGS AND PRECAUTIONS- 7.1 Special Populations, 7.1.1 Pregnant Women](#)).

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, skin exfoliation/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.

7.1 Special Populations

7.1.1 Pregnant Women

METHOTREXATE SUBCUTANEOUS is contraindicated in pregnant patients (see [2 CONTRAINDICATIONS](#) and [7 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 SUBCUTANEOUS. Men should not donate semen during therapy or from 6 months to one year following discontinuation of METHOTREXATE SUBCUTANEOUS.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

The clinical pharmacology of methotrexate has not been well studied in older individuals (≥ 65 years of age). 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.

7.1.5 Renal Impairment

METHOTREXATE SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see [2 CONTRAINDICATIONS](#) and [4 DOSAGE AND ADMINISTRATION-Special populations](#)).

7.1.6 Hepatic Impairment

METHOTREXATE SUBCUTANEOUS is contraindicated in patients with alcoholism, alcoholic liver disease or other chronic liver disease.

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 in [7 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, thrombocytopenia, pancytopenia, agranulocytosis and severe courses of bone marrow depression, and 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, and 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/hypoaesthesia, 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 jirovecii* 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.

8.2 Clinical Trial Adverse Reactions

Not applicable.

8.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other

Quantitative Data

Abnormal hematologic and clinical chemistry findings are discussed in [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 3 Post-Market Adverse Reactions

System Organ Class	Adverse Reaction
Infections and Infestations	Infections (including fatal sepsis); Pneumonia; <i>Pneumocystis jirovecii</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 or other inactive chronic 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; Acute aseptic meningitis; Encephalopathy/ Leukoencephalopathy
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; Abdominal pain; Gastrointestinal ulcers and bleeding; Gingivitis
Hepatobiliary Disorders	Hepatic failure; Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase, and bilirubin)

System Organ Class	Adverse Reaction
Skin and Subcutaneous Tissue Disorders	Drug reaction with eosinophilia and systemic symptoms; Dermatitis; Petechiae; Injection site necrosis; Skin ulcer; Local skin reactions at site of injection (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain)
Musculoskeletal, Connective Tissue and Bone Disorders	Osteonecrosis; Stress fracture
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, Asthenia
Endocrine Disorders	Diabetes
Ophthalmologic Disorders	Transient blindness/vision loss
Psychiatric Disorders	Mood alterations

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 DRUG INTERACTIONS- Drug-Drug Interactions](#))

9.2 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.

9.3 Drug-Behavioural Interactions

Use of alcohol with METHOTREXATE SUBCUTANEOUS is contraindicated (see [2 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.

9.4 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).

Table 4 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Nonsteroidal 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 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

Proper/Common name	Source of Evidence	Effect	Clinical comment
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.
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 SUBCUTANEOUS are given concurrently.
Ciprofloxacin	T	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.	Use with caution.
Mercaptopurine	T	Methotrexate increases the plasma levels of mercaptopurine.	Combination of METHOTREXATE SUBCUTANEOUS and mercaptopurine may therefore require dose adjustment.
Leflunomide	T	Methotrexate in combination with leflunomide may increase the risk of pancytopenia.	Use with caution.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs Highly Bound to Plasma Proteins, such as sulfonyleureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol	T	Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs.	Use with caution.
Probenecid	T	Renal tubular transport is also diminished by probenecid.	Use of METHOTREXATE SUBCUTANEOUS with this drug should be carefully monitored.
Nephrotoxic Drugs, such as aminoglycoside, Amphotericin B and Cyclosporin	T	Although not documented, other nephrotoxic drugs could theoretically increase methotrexate toxicity by decreasing its elimination.	Use with caution.
Penicillins and Sulfonamides	C, CT, T	Penicillins and sulfonamides may reduce the renal clearance of METHOTREXATE SUBCUTANEOUS; hematologic and gastrointestinal toxicity have been observed in combination with methotrexate.	Use with caution.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral Antibiotics, such as such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics	C, T	<p>Oral 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.</p> <p>For example: Neomycin, Polymyxin B, Nystatin and Vancomycin decrease methotrexate absorption, whereas Kanamycin increases methotrexate absorption.</p> <p>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.</p>	Use with caution.
Theophylline	T	METHOTREXATE SUBCUTANEOUS may decrease the clearance of theophylline.	Theophylline levels should be monitored when used concurrently with METHOTREXATE SUBCUTANEOUS

Proper/Common name	Source of Evidence	Effect	Clinical comment
Vitamins, such as folic acid or folinic acid	T	<p>Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered METHOTREXATE SUBCUTANEOUS.</p> <p>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.</p> <p>Folate deficiency states may increase methotrexate toxicity.</p>	<p>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.</p>
Hepatotoxins	C	<p>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.</p>	<p>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.</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
Proton Pump Inhibitors (PPI)	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.
Amiodarone	C	Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions.	
Diuretics	C	Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.	
Psoralen Plus Ultraviolet Light (PUVA) Therapy	C	Skin cancer has been reported in few patients with psoriasis receiving a concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).	

Proper/Common name	Source of Evidence	Effect	Clinical comment
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 methotrexate) and nephritis (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS- Renal).	In case of accidental co-administration, this effect can be reduced by the use of leucovorin rescue.

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

Interactions with herbal products have not been established.

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 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.

10.2 Pharmacodynamics

Methotrexate interferes with DNA synthesis, repair, and cellular replication. 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 this effect of methotrexate.

In patients with rheumatoid arthritis, methotrexate shows good overall efficacy for signs and symptoms, inhibition of structural damage and preservation of function with acceptable and manageable safety. Effects on articular swelling and tenderness can be seen as early as three to six weeks.

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.

10.3 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 synthases. 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. 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 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.

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.

11 STORAGE, STABILITY AND DISPOSAL

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 METHOTREXATE SUBCUTANEOUS should be disposed in line with local regulations for hazardous drugs. Syringes must be discarded after use in a sharp's container.

12 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

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Methotrexate

Chemical name: Methotrexate

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

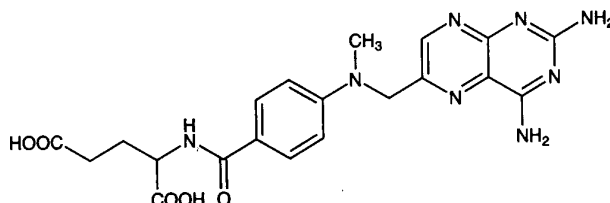
Amethopterin

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:

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.

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.

14 CLINICAL TRIALS

No data available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Results of a 22 month study in rats, receiving 0.1, 0.2 and 0.4 mg methotrexate/kg/day, 5 days/week every other week showed, 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 $2 \times 10^{-8} \text{M}$. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate resulting in plasma levels in excess of $2 \times 10^{-8} \text{M}$ 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.

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. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered not classifiable as to its carcinogenicity to humans.

Genotoxicity: There is evidence that methotrexate is mutagenic in vivo and in vitro. It causes chromosomal damage to animal somatic cells and human bone marrow cells.

Reproductive and Developmental Toxicology: No reproductive toxicology studies have been performed. Animal studies show that methotrexate impairs fertility, is embryo - and foetotoxic and teratogenic.

Data are available regarding the risks for pregnancy and for fertility in humans (see [7. WARNINGS AND PRECAUTIONS - 7.1 Special Populations, 7.1.1 Pregnant Women](#)).

Special Toxicology: No special toxicology studies have been performed.

Juvenile Toxicity: No juvenile toxicology studies have been performed.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrMETOJECT® SUBCUTANEOUS, solution, 50 mg / mL methotrexate (as methotrexate sodium), submission control 251944, Product Monograph, Medexus Inc. (DEC 07, 2021).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **METHOTREXATE SUBCUTANEOUS** **Methotrexate Injection BP**

Read this carefully before you start taking **METHOTREXATE SUBCUTANEOUS** 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 **METHOTREXATE SUBCUTANEOUS**.

Serious Warnings and Precautions

- **METHOTREXATE SUBCUTANEOUS** should be prescribed by a healthcare professional who is experienced with the use of methotrexate.
- Only take **METHOTREXATE SUBCUTANEOUS** **once a week**. If not taken properly, **METHOTREXATE SUBCUTANEOUS** can cause serious side effects which may cause death.

Pregnancy and Breastfeeding: Female Patients:

- **METHOTREXATE SUBCUTANEOUS** can harm your unborn baby and cause birth defects. This can lead to miscarriage or abortion.
- Do not use **METHOTREXATE SUBCUTANEOUS** if you are pregnant, or plan on getting pregnant during or after treatment. If you want to get pregnant, talk to your healthcare professional for advice.
- If you are able to become pregnant:
 - A pregnancy test will be taken before treatment. More tests might be needed during treatment to make sure you are not pregnant.
 - Use birth control during your treatment and for at least 6 months to 1 year after your last dose.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant.
- Do not breastfeed before and during treatment with **METHOTREXATE SUBCUTANEOUS**.

Male patients:

- Do not father a child while you are taking **METHOTREXATE SUBCUTANEOUS**.
- Use effective birth control during your treatment and for at least 6 months to 1 year after your last dose.
- If, during your treatment, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.
- You should not donate sperm during treatment for at least 6 months to 1 year after your last dose.

What is **METHOTREXATE SUBCUTANEOUS used for?**

METHOTREXATE SUBCUTANEOUS is used to treat adults with the following severe disabling conditions when other treatments do not work:

- psoriasis (a skin disease).
- psoriatic arthritis (joint inflammation that affects people with psoriasis).
- rheumatoid arthritis (joint inflammation caused by the immune system).

How does **METHOTREXATE SUBCUTANEOUS work?**

METHOTREXATE SUBCUTANEOUS therapy helps control psoriasis and rheumatoid arthritis but it will not cure them. Some normal cells in the body may be affected as well.

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

What are the ingredients in **METHOTREXATE SUBCUTANEOUS?**

Medicinal ingredients: Methotrexate.

Non-medicinal ingredients: Sodium chloride, sodium hydroxide and water for injection.

METHOTREXATE SUBCUTANEOUS comes in the following dosage forms:

- METHOTREXATE SUBCUTANEOUS (methotrexate injection) 50 mg / mL (as methotrexate sodium) is available in single-use USP type I glass 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	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.
- The carton and the finger-grip on the syringe are colour-coded to match.

Do not use METHOTREXATE SUBCUTANEOUS if you:

- Are allergic to methotrexate or any ingredient of the drug or container
- Have severe kidney problems, including kidney failure or kidney stones.
- Are on dialysis
- Are pregnant or plan on getting pregnant
- Are breast-feeding
- Suffer from alcoholism, alcoholic liver disease or other liver problems (including hepatitis B or C).
- Have immune system problems (immunodeficiency diseases)
- Have blood or bone marrow problems
- 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 METHOTREXATE SUBCUTANEOUS. Talk about any health conditions or problems you may have, including if you:

- Have problems with fluid build-up in your body.
- Have any blood or bone marrow problems including:
 - Low levels of blood cells called platelets (thrombocytopenia).
 - Low red blood cells (anemia).
 - Low levels of white blood cells (neutropenia, leukopenia)
- Have inflamed blood vessels.
- Have cancer or tumours.
- Have an infection.
- Were recently vaccinated.
- Are dehydrated or have a lot of vomiting, diarrhea, or sweating.
- Are obese.
- Have diabetes.
- Have stomach ulcers.
- Have inflammatory bowel disease (ulcerative colitis).
- Have mouth sores or inflammation.
- Have a history of gout (a type of arthritis).
- Have or had a recent exposure to chicken pox or shingles.
- Been treated with radiation.

Other warnings you should know about:

METHOTREXATE SUBCUTANEOUS can cause:

- **Blood and bone marrow problems** and can cause infections and affect your blood clotting. To reduce the risk of infection or bleeding, you should:
 - Avoid people with infections. Check with your healthcare professional right away 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 hard urination.
 - Check with your healthcare professional right away if you notice any abnormal bleeding or bruising; black, tarry stools; blood in urine or stools; or red spots on your skin.
 - Be careful when using a regular toothbrush, dental floss, or toothpick. Check with your healthcare professional 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 can happen.
- **Kidney problems.** Your healthcare professional may want you to drink extra fluids so that you will pass more urine. This will help prevent kidney problems and keep your kidneys working well.

METHOTREXATE SUBCUTANEOUS can also cause **gastrointestinal, liver, lung, nervous system** and **skin problems**. See the “Serious side effects and what to do about them” table, below, for more information on these and other serious side effects.

Immune system and vaccines:

- METHOTREXATE SUBCUTANEOUS can affect your immune system. It can prevent your body from making antibodies that help avoid infections.
- METHOTREXATE SUBCUTANEOUS can make diseases such as shingles or tuberculosis come back.
- Vaccines might not be effective during treatment. Rare infections related to vaccines can occur. You should not get any vaccines during treatment with METHOTREXATE SUBCUTANEOUS.
- 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.

Female fertility: METHOTREXATE SUBCUTANEOUS can cause abnormal periods and other vaginal bleeding problems for a short time during and after treatment. It can also affect your eggs.

Male fertility: METHOTREXATE SUBCUTANEOUS can lower sperm count for a short time during and after treatment.

Children (less than 18 years old): METHOTREXATE SUBCUTANEOUS is not for use in children.

Elderly (65 years or older): Side effects may happen more often. Your healthcare professional will monitor your health during and after treatment.

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will do blood tests to check your liver and kidney health, liver biopsies, lung tests and/or chest x-rays.

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

Serious Drug Interactions

Do not take METHOTREXATE SUBCUTANEOUS if you are going to receive nitrous oxide (laughing gas).

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

The following may interact with METHOTREXATE SUBCUTANEOUS:

- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) such as acetylsalicylic acid (ASA, Aspirin)
- Leflunomide, used to treat rheumatoid arthritis or Disease Modifying Antirheumatic Drugs (DMARDs), such as gold, penicillamine, hydroxychloroquine, or sulfasalazine
- Medicines used to treat bacterial and fungal infections (such as antibiotics and amphotericin B), or to prevent malaria (such as pyrimethamine)
- Medicines used to treat leukemia, such as cytarabine and mercaptopurine
- Medicines used to treat stomach problems (proton pump inhibitors (PPI)) such as omeprazole, esomeprazole, and pantoprazole.
- Immunosuppressants such as azathioprine, cyclosporin
- Probenecid, used to treat gout
- Retinoid medicines, used to treat acne
- Sulfonylureas, used to treat diabetes
- Theophylline, used to treat respiratory diseases
- Vitamins such as folic acid and folinic acid
- Phenytoin, used to treat seizures
- Amiodarone, used to treat irregular heart beat
- Triamterene, used as a diuretic or “water pill”
- Packed red blood cells, used for blood transfusions.
- Radiotherapy, a type of cancer treatment
- Psoralen Plus Ultraviolet Light (PUVA) therapy, used to treat skin conditions

Tell any healthcare professional that is treating you that you are taking METHOTREXATE SUBCUTANEOUS.

How to take METHOTREXATE SUBCUTANEOUS:

- **Always use METHOTREXATE SUBCUTANEOUS exactly as your healthcare professional has shown you.**
- **Read the “INSTRUCTIONS FOR USE FOR METHOTREXATE SUBCUTANEOUS SELF-INJECTION” section every time before you inject METHOTREXATE SUBCUTANEOUS.** Check with your healthcare professional if you are not sure.
- Do not take more or less of it, and do not take it more often than your healthcare professional has told you.
- METHOTREXATE SUBCUTANEOUS is injected under the skin **once a week**.
- At the start of your treatment, METHOTREXATE SUBCUTANEOUS will be injected by your healthcare professional.
 - Your healthcare professional might train you or your caregiver on how to inject METHOTREXATE SUBCUTANEOUS under the skin.
 - **Do not try to inject METHOTREXATE SUBCUTANEOUS until you or your caregiver have received proper training.**
 - **Ask your healthcare professional any questions you may have.**
- Pregnant or breast-feeding healthcare professionals or caregivers should not handle and/or inject METHOTREXATE SUBCUTANEOUS.
- Each METHOTREXATE SUBCUTANEOUS syringe can be used once. It must be thrown away after use in a sharps container.

Usual dose:

- The dose of METHOTREXATE SUBCUTANEOUS will be different for different patients.

- The dose depends on what the medicine is being used for, your weight, and if you are taking other medicines.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
 - experience serious side effects, or
 - your disease gets worse.

Overdose:

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

Missed Dose:

- If you missed a dose of METHOTREXATE SUBCUTANEOUS, the next dose should be taken as soon as possible.
- Ask your healthcare professional if you have questions about missed doses.

What are the possible side effects from using METHOTREXATE SUBCUTANEOUS?

These are not all the possible side effects you may have when taking METHOTREXATE SUBCUTANEOUS. If you experience any side effects not listed here, tell your healthcare professional.

METHOTREXATE SUBCUTANEOUS might cause other unwanted effects that may not occur until months or years after it is used. These delayed effects may include certain types of cancer, such as leukemia. Discuss these possible effects with your healthcare professional.

- | | |
|---|--|
| • Tiredness, weakness or dizziness | • Change in voice (hoarseness) |
| • Chills and fever | • Skin rashes, pin-point red spots on the skin, reddening or whitening of the skin, acne, boils |
| • Headaches | • Lower sex drive, decreased fertility |
| • Hair loss | • Abnormal vaginal bleeding, missed periods, vaginal discharge |
| • Ringing in the ears | • Injection Site Reactions: blistering, itching, pain, redness, severe skin damage, tenderness, build up of pus and fat, warmth in the area around the injection |
| • Mood changes, fits, confusion | • Swelling in areas of the body that do not involve the injection sites. |
| • Nervous system problems: abnormal reflexes, paralysis, difficulty speaking, loss of consciousness, disorientation, reduced senses of touch or temperature, numbness or feelings of prickling (pins and needles) | • Thin, fragile bones, muscle and joint pain |
| • Sore eyes, short term blindness | • Diabetes |
| • Inflamed gums | |
| • Stomach/abdominal pain, indigestion, loss of appetite | |

METHOTREXATE SUBCUTANEOUS causes nausea and vomiting. Even if you begin to feel ill, do not stop using this medicine without first checking with your healthcare professional.

Methotrexate can cause abnormal blood and urine test results. Your healthcare professional will do these tests before, during and after treatment. These will tell your healthcare professional how METHOTREXATE SUBCUTANEOUS is affecting your blood, liver and 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	
COMMON			
Blood problems (low white, red, and/or platelet blood cell counts): shortness of breath, weakness, frequent infections, cold sores, pale skin, rapid heart rate, fever, bruising easily and heavy bleeding, or bleeding for longer than usual if you hurt yourself		√	
Gastrointestinal problems: diarrhea, vomiting, dehydration, blood in stool, bloody vomit, black tarry stools	√		
Lung problems: Pneumonitis / Pneumonia (lung inflammation/infection): fever, chest pain, sweating and shaking chills, persistent dry, non-productive cough, shortness of breath		√	
Sepsis and septic shock (blood infections): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, rapid breathing and heart beat		√	
RARE			
Anaphylactic shock (severe allergic reaction): chest tightness, wheezing, dizziness, faintness, rapid heartbeat, shortness of breath, and/or a swollen face, lips, tongue, or gums			√
Kidney problems: Pain or difficulty urinating, lower back or side pain, blood in urine, dark urine		√	
Liver problems (including Hepatitis): yellowing of your skin and eyes, right upper stomach area pain or swelling, nausea or vomiting, dark urine		√	
Osteonecrosis (tiny breaks in a bone leading to eventual collapse): broken bones, jaw pain (bone damage in the jaw)		√	
Pericarditis, Pericardial effusion (inflammation of the lining or build-up of fluid around the heart): chest pain or pressure, shortness of breath, sharp, stabbing chest pain that gets worse when you cough, swallow, breathe deeply or lie flat		√	
VERY RARE			
Acute gastric dilation (enlarged stomach): nausea, vomiting or inability to vomit, bloating/distension in the abdomen area, sudden onset of abdominal pain		√	
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): confusion, sudden headache or stiffness of your neck, sensitivity to light			√
Lymphoma (lymphatic system cancer): painless swelling of lymph node/glands, swollen tonsils, night sweats, itching, unexplained weight loss, persistent coughing/difficulty breathing or not being able to breathe		√	

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	
Skin problems: Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), Erythema multiforme (severe skin reactions): redness, blistering and/or peeling of large areas of the skin, raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			√
UNKNOWN			
Nervous system problems: Leukoencephalopathy / Encephalopathy (neurological/brain disorder): seizures, confusion, speech and visual loss, changes in thinking, memory and orientation, personality changes		√	
Pulmonary alveolar haemorrhage (bleeding in the lungs): 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 METHOTREXATE SUBCUTANEOUS between 15 to 25°C in original carton. Store away from heat and light. Avoid freezing.
- Keep out of the reach and sight of children.
- Do not keep outdated medicine or medicine no longer needed. Throw away any unused solution.
- 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.

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 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.accordhealth.ca), or by calling 1-866-296-0354.

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INSTRUCTIONS FOR USE FOR METHOTREXATE SUBCUTANEOUS SELF-INJECTION:

Follow these instructions with all doses of METHOTREXATE SUBCUTANEOUS. Check the packaging to make sure that you have the right syringe. It should match the dose your doctor has told you to take.

⚠ 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).

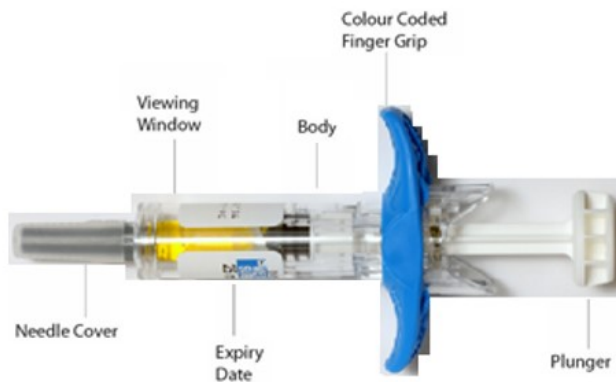
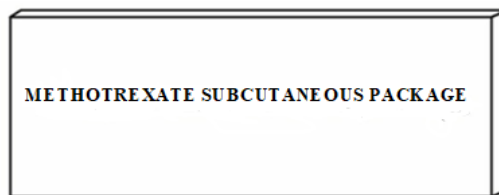


Figure A

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

STEP I: SETTING UP

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




Sharps container for safe disposal of used needles and syringes

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.
- An empty detergent bottle or coffee can may be used.

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), 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 a caregiver only): Give the injection into the back of the upper arm, just below the shoulder.

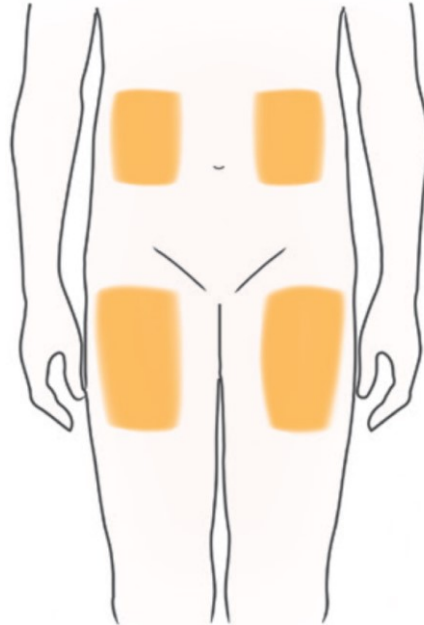


Figure C



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 area of and around 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 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).

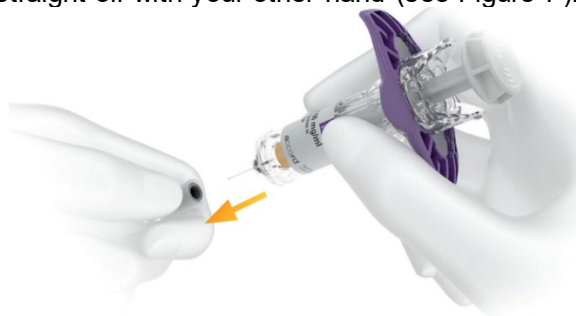



Figure F

- **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.

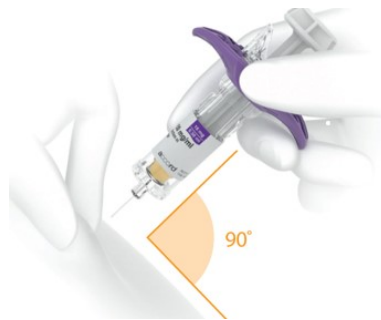


Figure G

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 (see 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.

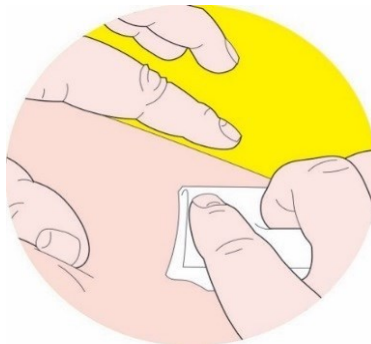


Figure K

3. Methotrexate should not come into contact with the surface of the skin or mucosa. If this happens, rinse immediately with plenty of water.

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** throw away the used syringe in your household trash.
-  **Do not** reuse the syringe. The syringe must be discarded after use.
-  **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

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