PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMETOJECT® 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

House Standard

Immunosuppressant

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RECENT MAJOR LABEL CHANGES

7. Warnings and Precautions	12/2021
8. Adverse Reactions	12/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

METOJECT 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, METOJECT 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
METOJECT 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

METOJECT 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

- METOJECT 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).
- METOJECT SUBCUTANEOUS must be administered **only once a week**. Dosage errors in the use of METOJECT SUBCUTANEOUS (methotrexate injection) can result in serious adverse reactions, including death.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

METOJECT 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 METOJECT 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: METOJECT 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: METOJECT 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

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

4.4 Administration

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

METOJECT SUBCUTANEOUS solution should be yellow-brown in colour and should be clear with no particles in it. Visually inspect METOJECT SUBCUTANEOUS for particulate matter and discolouration prior to administration. Do not use METOJECT 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 overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

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

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

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

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

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

METOJECT SUBCUTANEOUS is a clear, yellow-brown solution that is free of particles.

METOJECT 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, 4, or 12 single-use 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

METOJECT 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.

METOJECT 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 METOJECT 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 METOJECT 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.

METOJECT 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 **NON-CLINICAL TOXICOLOGY**.

Gastrointestinal

If vomiting, diarrhea, or stomatitis occurs, resulting in dehydration, METOJECT 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. METOJECT 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 METOJECT SUBCUTANEOUS (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

METOJECT SUBCUTANEOUS should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. METOJECT 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/mm^3) was seen in 2 patients, thrombocytopenia (platelets <1,000,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, METOJECT 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 METOJECT SUBCUTANEOUS (usually in high dosage) along with some non-steroidal anti-inflammatory drugs (NSAIDs) (see **9 DRUG** INTERACTIONS).

Hepatic/Biliary/Pancreatic

METOJECT SUBCUTANEOUS has the potential for acute and chronic hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after METOJECT SUBCUTANEOUS administration and are usually not a reason for modification of METOJECT 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 (Roenigk grades I, II, IIIa), METOJECT SUBCUTANEOUS may be continued and the patient monitored according to the recommendations listed above. METOJECT 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 (Roenigk grade IIIb or IV).

There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Immune

METOJECT 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 METOJECT SUBCUTANEOUS therapy are not indicated routinely. Liver function tests (LFTs) should be determined prior to the initiation of therapy with METOJECT 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 METOJECT SUBCUTANEOUS 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 METOJECT 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 alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Nephritis has been reported on co-administration with nitrous oxide anesthesia in rheumatoid arthritis patients (see **2** CONTRAINDICATIONS and **9 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

METOJECT SUBCUTANEOUS therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* 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 METOJECT 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 METOJECT 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

METOJECT SUBCUTANEOUS is contraindicated in pregnant patients (see **2** CONTRAINDICATIONS and **7 WARNINGS AND** PRECAUTIONS). METOJECT

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 METOJECT SUBCUTANEOUS.

Women of childbearing potential should not be started on METOJECT 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 METOJECT 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.

7.1.2 Breast-feeding

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, METOJECT 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

METOJECT SUBCUTANEOUS is contraindicated in patients with severe renal impairment (see **2** CONTRAINDICATIONS and **4 DOSAGE AND** ADMINISTRATION-**Special populations**).

7.1.6 Hepatic Impairment

METOJECT 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, 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, haematorrhea 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/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; *Pneumocystis jirovecii* pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; *H. simplex* hepatitis; Disseminated *H. simplex*; 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 **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 METOJECT 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 METOJECT 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 METOJECT SUBCUTANEOUS are given concurrently.
Ciprofloxacin	T	Renal tubular transport is diminished by ciprofloxacin.	Use of METOJECT 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 METOJECT 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 sulfonylureas, 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 METOJECT 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 METOJECT SUBCUTANEOUS toxicity by decreasing its elimination.	Use with caution.
Penicillins and Sulfonamides	C, CT, T	Penicillins and sulfonamides may reduce the renal clearance of METOJECT SUBCUTANEOUS; hematologic and gastrointestinal toxicity have been observed in combination with METOJECT SUBCUTANEOUS	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	Oral antibiotics may decrease intestinal absorption of METOJECT 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 METOJECT SUBCUTANEOUS absorption, whereas Kanamycin increases METOJECT SUBCUTANEOUS absorption. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving METOJECT SUBCUTANEOUS, probably by decreased tubular secretion and/or an additive antifolate effect.	Use with caution.
Theophylline	T	METOJECT SUBCUTANEOUS may decrease the clearance of theophylline.	Theophylline levels should be monitored when used concurrently with METOJECT SUBCUTANEOUS

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Vitamins, such as folic acid or folinic acid	T	Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered METOJECT 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. Folate deficiency states may increase METOJECT SUBCUTANEOUS toxicity.	Before taking a folate supplement, it is advisable to check B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B_{12} deficiency.
Hepatoxins	C	The potential for increased hepatotoxicity when METOJECT SUBCUTANEOUS is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases.	~~Therefore,~~ ~~p~~Patients receiving concomitant therapy with METOJECT SUBCUTANEOUS and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

[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 syntheses. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumours. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Elimination: Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. 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 METOJECT 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 METOJECT 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 METOJECT SUBCUTANEOUS.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Methotrexate

Chemical name: Methotrexate

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

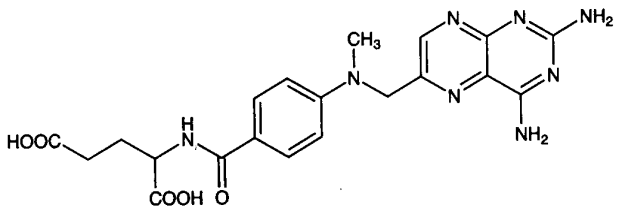
Amethopterin

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

4-Amino-10-methylfolic acid

Molecular formula
and molecular mass: $C_{20}H_{22}N_8O_5$ (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 $C_{20}H_{22}N_8O_5$ calculated on the anhydrous basis. The parenteral solution is prepared with the sodium salt, but potency is always expressed on the basis of the acid.

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

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

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 $2x10^{-8}$M. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate resulting in plasma levels in excess of $2x10^{-8}$M circulating for greater than 42 hours will be toxic to both the bone marrow and gastrointestinal epithelium. This toxicity can be minimized by the appropriate administration of Leucovorin Calcium.

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

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.