

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metoject 10 mg/ml solution for injection, pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 10 mg methotrexate (as methotrexate disodium).

1 pre-filled syringe of 0.75 ml contains 7.5 mg methotrexate

1 pre-filled syringe of 1 ml contains 10 mg methotrexate

1 pre-filled syringe of 1.5 ml contains 15 mg methotrexate

1 pre-filled syringe of 2 ml contains 20 mg methotrexate

1 pre-filled syringe of 2.5 ml contains 25 mg methotrexate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoject is indicated for the treatment of:

- Severe, active rheumatoid arthritis in adult patients
- Polyarthritic forms of severe, active juvenile idiopathic arthritis when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate
- Severe and generalised psoriasis vulgaris, especially plaque-type, and psoriatic arthritis in adult patients which are unresponsive to conventional therapy.

4.2 Posology and method of administration

Metoject should only be prescribed by physicians, who are familiar with the various characteristics of the medicinal product and its mode of action. Metoject is injected once weekly.

Dosage in adult patients with rheumatoid arthritis:

The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. 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. Response to treatment can be expected after approximately 4 -8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients with psoriasis vulgaris and psoriatic arthritis:

It is recommended that a test dose of 5-10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Response to treatment can generally be expected after approximately 2 - 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Patients with renal impairment:

Metoject should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)

>50	100%
20-50	50%
<20	Metoject must not be used

Patients with hepatic impairment:

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated.

Use in elderly patients:

Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age.

Dosage in children below 16 years with polyarthritic forms of juvenile idiopathic arthritis:

The recommended dose is 10-15 mg /m² body surface area (BSA)/week. In case of insufficient efficacy the weekly dosage may be increased to up to 20 mg/m² BSA/week. Due to the limited data of subcutaneous and intravenous use in children the use in juvenile idiopathic arthritis is limited to intramuscular injection.

Duration and method of administration

Metoject injection can be given by intramuscular, intravenous or subcutaneous route.

The overall duration of the treatment is decided by the physician.

Note:

If changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications

Metoject is contra-indicated in the case of:

- hypersensitivity to methotrexate or to any of the excipients,
- liver insufficiency (see also 4.2 Posology and method of administration),

- alcohol abuse,
- renal insufficiency (creatinine clearance less than 20 ml/min., see also 4.2 Posology and method of administration),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis and HIV, ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy, breast-feeding (see also 4.6 Pregnancy and lactation).
- concurrent vaccination with live vaccines

4.4 Special warnings and precautions for use

Patients must be clearly informed, that the therapy has to be applied once a week, not every day.

Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore Methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Recommended examinations and safety measures:

Before beginning or reinstating Methotrexate therapy after a rest period: Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter):

An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes.

Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicate immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

2. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications. For psoriasis patients the need of a liver biopsy prior to and during therapy should be evaluated according to current scientific knowledge. The evaluation should differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of

liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals.

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see 4.5 Interactions with other medicinal products and other forms of interaction.). Closer monitoring of liver enzymes should be exercised in Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

3. Renal function should be monitored by renal function tests and urinalysis.

As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects.

Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

4. Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. 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 dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. This lesion can occur at all dosages.

5. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Concurrent vaccination using live vaccines should not be carried out .

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

The absence of pregnancy should be confirmed before Metoject is administered.

Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility. These effects appear to be reversible on discontinuing therapy. Effective contraception in men and women should be performed during treatment and for at least six months thereafter. The possible risks of effects on reproduction should be discussed

with patients of childbearing potential and their partners should be advised appropriately (see 4.6 Pregnancy and lactation).

4.5 Interactions with other medicinal products and other forms of interaction

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products

The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see 4.4 Special warnings and precautions for use.). Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Oral antibiotics

Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics

Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents

Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity. There is also a possibility of increased toxicity when low dose methotrexate and non steroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse reactions on the bone marrow

In the case of medication with medicinal products, which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency

The concomitant administration of products which cause folate deficiency (e. g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

Other antirheumatic medicinal products

An increase in the toxic effects of methotrexate is, in general, not to be expected when Metoject is administered simultaneously with other antirheumatic medicinal products (e. g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprin, cyclosporin).

Sulphasalazine

Although the combination of methotrexate and sulphasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulphasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Proton-pump inhibitors

A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Caffeine- or theophylline-containing beverages

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing softdrinks, black tea) should be avoided during methotrexate therapy.

4.6 Pregnancy and lactation

Metoject is contra-indicated during pregnancy (see 4.3 Contra-indications). In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see 5.3 Preclinical safety data). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported. Women must not get pregnant during methotrexate therapy. In case of women getting pregnant during therapy medical counselling about the risk of adverse reactions for the child associated with methotrexate therapy should be sought. Therefore, patients of a sexually mature age (women and men) must use effective contraception during treatment with Metoject and at least 6 months thereafter (see 4.4 Special warnings and precautions for use).

Lactation: Methotrexate is excreted in breast milk in such concentrations that there is a risk for the infant, and accordingly, breastfeeding should be discontinued prior to and throughout administration.

4.7 Effects on the ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, Metoject has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:

Very common ($\geq 1/10$), common ($\geq 1/100$; $< 1/10$), uncommon ($\geq 1/1,000$; $< 1/100$), rare ($\geq 1/10,000$; $< 1/1,000$) and very rare ($< 1/10,000$).

Gastrointestinal disorders

Very common: Stomatitis, dyspepsia, nausea, loss of appetite.

Common: Oral ulcers, diarrhoea.

Uncommon: Pharyngitis, enteritis, vomiting,

Rare: Gastrointestinal ulcers.

Very rare: Hematemesis, hematorrhea

Skin and subcutaneous tissue disorders

Common: Exanthema, erythema, pruritus.

Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.

Rare: Increased pigmentation.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia.

General disorders and administration site conditions

Rare: Allergic reactions, anaphylactic shock; allergic vasculitis, fever, conjunctivitis, infection, sepsis, wound-healing impairment, pleural effusion, pericardial effusion, pericardial tamponade, hypogammaglobinaemia.

Nervous system disorders

Common: Headache, tiredness, drowsiness.

Uncommon: Dizziness, confusion, depression.

Very rare: Impaired vision, pain, muscular asthenia or paresthesia in the extremities, changes in sense of taste (metallic taste), convulsions, meningism, paralysis.

Hepatobiliary disorders

Very common: Elevated transaminases.

Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver.

Respiratory, thoracic and mediastinal disorders

Common: Interstitial alveolitis/pneumonitis. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.

Rare: Pulmonary fibrosis, *Pneumocystis carinii* pneumonia, shortness of breath and bronchial asthma.

Blood and lymphatic system disorders

Common: Leukopenia, anaemia, thrombopenia.

Uncommon: Pancytopenia.

Very rare: Agranulocytosis, severe courses of bone marrow depression.

Renal and urinary disorders

Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.

Rare: Renal failure, oliguria, anuria, electrolyte disturbances.

Reproductive system and breast disorders

Uncommon: Inflammation and ulceration of the vagina.

Very rare: Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge.

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, myalgia, osteoporosis.

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

Very rare: There have been reports of individual cases of lymphoma which subsided in a number of cases once treatment with methotrexate had been discontinued. In a recent study, it could not be established that methotrexate therapy increases the incidence of lymphomas.

The appearance and degree of severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) can occur at the site of injection.

4.9 Overdose

a) Symptoms of overdosage

Toxicity of methotrexate mainly affect the haematopoietic system.

b) Treatment measures in the case of overdosage

Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

In cases of massive overdose, hydration and urinary alkalinisation it may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues, other immunosuppressants.

ATC code: L01BA01, L04AX03

Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis.

Methotrexate is a folic acid analogue which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis and chronic polyarthritis, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

5.2 Pharmacokinetic properties

Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts. The terminal half-life is on average 6 - 7 hours and demonstrates considerable variation (3 - 17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus.

Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary. Pronounced enterohepatic blood flow exists.

In the case of renal insufficiency, elimination is delayed significantly. Impaired elimination with regard to hepatic insufficiency is not known.

5.3 Preclinical safety data

Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic in vivo and in vitro. Rodent carcinogenicity studies do not indicate an increased incidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium hydroxide for pH adjustment

Water for injections

6.2 Incompatibilities

Compatibility with other parenteral products has not been studied. It is recommended that this formulation is not mixed with other medicinal products or diluents.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store below 25°C. Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Nature of container:

Pre-filled syringe of colourless glass (type I) of 1, 2.25, 3 ml capacity with or without injection needle adapter and elastomeric tip cap, plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger.

Pack sizes:

Pre-filled syringes containing 0.75 ml, 1 ml, 1.5 ml, 2 ml or 2.5 ml solution are available in packs of 1, 5, 10 or 30 syringes.

All pack sizes are available with graduation, with and without injection needles or with injection needles and alcohol pads.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Metoject.

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with ample amount of water.

For single use only. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstraße 3
D-20354 Hamburg

8. MARKETING AUTHORISATION NUMBER

16896

9. DATE OF FIRST MARKETING AUTHORISATION/RENEWAL OF THE AUTHORISATION

2002-05-03 / 2007-05-03

10. DATE OF REVISION OF THE TEXT

2009-05-26