# 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 the 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 where treatment with disease modifying antirheumatic drugs (DMARD) is indicated.

### 4.2 Posology and method of administration

Metoject should only be prescribed by physicians and administered by health professionals, who are familiar with the various characteristics of the medicinal product and its mode of action. Metoject is injected once weekly.
Careful monitoring should be undertaken after the first dose of methotrexate to exclude idiosyncratic hypersensitivity reactions.

Posology

*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 dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should not be exceeded. However, doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. 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.

*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 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.

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

Method of administration

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

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

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

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

## 4.3 Contraindications

Metoject is contraindicated in the case of:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe liver insufficiency (see also section 4.2),
- alcohol abuse,
- severe renal insufficiency (creatinine clearance less than 20 ml/min., see also section 4.2),
- pre-existing blood dycrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- severe 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 section 4.6),
- concurrent vaccination with live vaccines,
- immunodeficiency syndromes.

## 4.4 Special warnings and precautions for use

Patients have to be clearly informed, that Metoject must be administered 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 only be 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 of the risks involved and the recommended safety measures. However, doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression.

Recommended examinations and safety measures

*Before beginning methotrexate therapy or re-instituting 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, tuberculosis and hepatitis should be excluded.

*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.

2. 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 indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. 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.

   However, due to the hepatotoxic potential of methotrexate the need of a liver biopsy should be evaluated for risk patients with long-term use of methotrexate. Risk factors are primarily:
   – Excessive prior alcohol consumption
   – Persistent elevation of liver enzymes
   – Anamnestical liver diseases
   – Hereditary liver diseases

   Monitoring of liver 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 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 minimised (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). This is also required during simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Renal function should be monitored by renal function tests and urinanalysis (see also sections 4.2 and 4.3): 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.

5. Respiratory system: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

   Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

   Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all dosages.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination and affect the results of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible 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.

Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Encephalopathy/leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose and is essentially “sodium-free”.

## 4.5 Interaction 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 section 4.4). Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. This is also required during simultaneous administration of haematotoxic medicinal products (e.g. leflunomide). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics
Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation of methotrexate, due to 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.

Medicinal products with high plasma protein binding
Methotrexate is plasma protein bound and may be displaced by other protein bound medicinal products such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

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. Hence, higher serum concentrations can be expected, inducing higher haematological toxicity. There is also a risk 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 cause bone marrow depression (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), attention should be paid to the possibility of pronounced impairment of blood formation.

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

Products containing folic acid or folinic acid
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

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
The combination of methotrexate and sulphasalazine may increase the efficacy of methotrexate, but at the same time induce more undesirable effects, due to the inhibition of folic acid synthesis by sulphasalazine. However, 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, tea) should be avoided during methotrexate therapy.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Metoject is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 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 extremities). If methotrexate is discontinued prior to conception, normal pregnancies have been reported.
Pregnancy should be excluded before treatment with Metoject is initiated.

Women must not get pregnant during methotrexate therapy. Therefore, patients of a sexually mature age (women and men) must use effective contraception during treatment with Metoject and at least 6 months thereafter.
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.

Breast−feeding
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.

Fertility
The possible risks of effects on reproduction should be discussed with patients of childbearing potential, and their partners should be advised appropriately.

Methotrexate has been reported to cause defective oogenesis, defective spermatogenesis, oligospermia, infertility, menstrual dysfunction and amenorrhoea in humans, during and for a period after cessation of therapy.

## 4.7 Effects on 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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.

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombocytopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes.

Nervous system disorders
Common: Headache, tiredness, drowsiness.
Uncommon: Dizziness, confusion, depression, cognitive dysfunction.
Very rare: Impaired vision, pain, muscular asthenia or paresthesia in the extremities, changes in sense of taste (metallic taste), convulsions, meningism, paralysis.
Not known: Leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Retinopathy.

Cardiac disorders
Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders
Rare: hypotension, thromboembolic events

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia; symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, non-productive cough, dyspnoea and fever.
Rare: Pulmonary fibrosis, *Pneumocystis carinii* pneumonia, dyspnoea and bronchial asthma, pleural effusion.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, reduced appetite.
Common: Oral ulcers, diarrhoea.
Uncommon: Pharyngitis, enteritis, vomiting.
Rare: Gastrointestinal ulcers, malabsorption.

Very rare: Hematemesis, hematorrhea, toxic megacolon.

Hepatobiliary disorders
Very common: Elevated transaminases.
Uncommon: Cirrhosis, liver atrophy, periportal fibrosis and fatty degeneration of the liver.

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

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.

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: Reduced libido, impotence, oligospermia, defective oogenesis, defective spermatogenesis, infertility, menstruation disturbances, vaginal discharge.

General disorders and administration site conditions
Very common: Local skin reactions (burning sensation, redness) of injection site following intramuscular or subcutaneous administration. Most of these reactions are of mild degree.
Rare: Allergic reactions, anaphylactic shock, allergic vasculitis, fever, conjunctivitis, infection, sepsis, wound-healing impairment, hypogammaglobulinaemia.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.

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 a physician at short intervals.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

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## 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. Early monitoring of methotrexate levels is recommended for dosage adjustment**.** Dosing should be continued until the serum levels of methotrexate are below $10^{-7}$ mol/l.

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid antagonist.
ATC code: L01BA01

Mechanism of action
Methotrexate is a folic acid antagonist 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 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

Distribution
Approximately 50 % of methotrexate is bound to serum proteins. Upon distribution into body tissues, high concentrations of polyglutamates are found in the liver, kidneys and spleen in particular, which can retain 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).

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

Elimination
Excretion takes places, mainly in unchanged form, primarily via glomerular filtration and active secretion in the proximal tubulus.
Approx. 5 – 20 % methotrexate and 1 – 5 % 7−hydroxymethotrexate are eliminated via the bile. There is a pronounced enterohepatic reuptake.

In the case of renal insufficiency, elimination is delayed significantly. It is not known whether hepatic insufficiency causes reduced methotrexate elimination.

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

## 6.2 Incompatibilities

In the absence of compatibility studies with other parenteral products, this medicinal product must not be mixed with other medicinal products or diluents.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Store below 25$^{o}$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:
Filling volumes: pre-filled syringes containing 0.75 ml, 1 ml, 1.5 ml, 2 ml or 2.5 ml solution.

Syringe sizes: pre-filled syringes (colourless glass, type I) of 1 ml, 2.25 ml and 3 ml, 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:
1, 5, 10 or 30 syringes.

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

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

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 must 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 medicinal product or waste material should be disposed of in accordance with local requirements.

# 7 MARKETING AUTHORISATION HOLDER

medac

Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

## 8 MARKETING AUTHORISATION NUMBER

PA0623/007/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First date of authorisation:31st March 2006

Last date of authorisation: 3rd May 2007

## 10 DATE OF REVISION OF THE TEXT

April 2014