Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metoject 15 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 pre-filled pen with 0.15 ml solution contains 7.5 mg methotrexate.
1 pre-filled pen with 0.20 ml solution contains 10 mg methotrexate.
1 pre-filled pen with 0.30 ml solution contains 15 mg methotrexate.
1 pre-filled pen with 0.40 ml solution contains 20 mg methotrexate.
1 pre-filled pen with 0.50 ml solution contains 25 mg methotrexate.

Excipients with known effect: sodium chloride and sodium hydroxide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.
Clear, yellow-brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoject is indicated for the treatment of
· active rheumatoid arthritis in adult patients,
· severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

4.2 Posology and method of administration

Important warning about the dosage of Metoject (methotrexate)
In the treatment of rheumatoid arthritis, and psoriasis and psoriatic arthritis, Metoject (methotrexate) must only be used once a week. Dosage errors in the use of Metoject (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Metoject should be performed under direct medical supervision.
Metoject is injected **once weekly**.

The patient must be explicitly informed about the fact that Metoject is administered **once a week only,** regardless of if used alone or in combination with other medicinal products. It is advisable to determine a fixed, appropriate weekday as day of injection.
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 (see section 5.2 and 4.4).

Posology

Posology in adult patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week.

A weekly dose of 25 mg should in general not be exceeded. Doses exceeding 20 mg/week are 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.

Paediatric population
Use in children <3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.4).

Posology 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 subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. 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.

Maximum weekly dose
The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

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)	**Dose**
≥60	100%
30–59	50%
<30	Metoject must not be used

See section 4.3.

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 micromol/l), methotrexate is contraindicated.

For the full list of contraindications, see section 4.3.

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 occur with increased age.

Use in patients with a third distribution space (pleural effusions, ascites)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see section 5.2 and 4.4).

Method of administration
The medicinal product is for single use only.
Metoject solution for injection in pre-filled pen can only be given by subcutaneous route.

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

Instructions for subcutaneous use of Metoject with yellow cap and yellow injection button (three-step auto-injector)
The most appropriate zones for the injection are:

- upper thighs,

- abdomen except around the navel.

1. Clean the area of and around the chosen injection site (e.g. with soap and water).
2. Pull the cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the Metoject is removed from the skin after the injection.
5. Push the Metoject firmly into the skin at a 90-degree angle in order to unlock the button. Then press the button (a click indicates the start of injection).
6. Do not remove the Metoject from the skin before the end of the injection to avoid incomplete injection. This can take up to 5 seconds.
7. Remove the Metoject from the skin at the same 90-degree angle.
8. The protective shield automatically moves into place over the needle and is then locked.

- **Instructions for subcutaneous use of Metoject with translucent protective cap and blue needle cover (two-step auto-injector)**

The most appropriate zones for the injection are:

- upper thighs,
- lower part of the abdomen except within 5 cm around the navel.

1. Clean the injection site.
2. Firmly pull the translucent cap straight off.
3. Position the uncapped blue needle cover at a 90-degree angle against the skin. It is not necessary to build a skin fold.
4. Start the injection by pushing the Metoject pen down all the way (a first "click" indicates the start of injection).
5. Continue holding the Metoject pen down against the skin to complete the injection until:
    - you hear a second "click", shortly after the first
    - or: the blue plunger rod has stopped moving and fills the inspection window
    - or: 5 seconds have passed.
6. Remove the Metoject pen from the skin at the same 90-degree angle.
7. The blue needle cover automatically moves into place over the needle and is then locked.

Please note that all of the contents have to be used.

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 contraindicated in the case of

· hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
· severe liver impairment (see section 4.2),
· alcohol abuse,
· severe renal impairment (creatinine clearance less than 30 ml/min., see section 4.2 and section 4.4),
· pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
· serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
· ulcers of the oral cavity and known active gastrointestinal ulcer disease,
· pregnancy, breast-feeding (see section 4.6),
· concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly informed that the therapy has to 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 treatment with methotrexate should only be initiated and supervised by 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 reinstituting 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

The tests below must be conducted every week during the first two weeks, then every two weeks for the next month; afterwards, depending on leukocyte count and stability of the patient, at least once monthly during the next six months and at least every three months thereafter.
Increased monitoring frequency should also be considered when increasing the dose. Particularly elderly patients should be examined for early signs of toxicity in short intervals.

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 doses. 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 taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. **Liver function tests**: Treatment should not be initiated or should be discontinued if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis, or liver biopsies.

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13–20%. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment.

Additional hepatotoxic medicinal products should not be given during treatment with methotrexate *unless clearly necessary*. Alcohol consumption should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.

Increased caution should be exercised in patients with insulin-dependent diabetes mellitus, as during methotrexate therapy, liver cirrhosis developed in isolated cases without any elevation of transaminases.

4. **Renal function** should be monitored by renal function tests and urine analysis (see 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 impairment, 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 that affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

5. 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. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. 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. Pulmonary diseases induced by methotrexate were not always completely reversible. This lesion can occur at all doses.
In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. 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.

6. 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. Vaccination using live vaccines must not be carried out under methotrexate therapy.

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.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or UV rays should be avoided unless medically indicated. Patients should use adequate sun-protection to protect themselves from intense sunlight.

Radiation-induced dermatitis and sunburn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

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. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

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.

For the treatment of psoriasis, methotrexate 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 by biopsy and/or after dermatological consultation.

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

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Fertility and reproduction

Fertility

Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk

Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Metoject is used. If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

Paediatric population

Use in children <3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Nitrous oxide
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

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. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). 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, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics

Antibiotics, like penicillins, 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 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 drugs 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. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

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.

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, sulfasalazine, azathioprine).

Cyclosporine

Cyclosporine may potentiate methotrexate efficacy and toxicity. There is an increased risk of renal dysfunction. In addition, there is a biological plausibility of excessive immunosuppression and its associated complications.

Sulfasalazine

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

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

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.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Caffeine- or theophylline-containing beverages

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. 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.

Contraception in males
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. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is 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 for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, 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 foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3).
Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal 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.

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Breastfeeding
Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, methotrexate is contraindicated during breastfeeding (see section 4.3). Therefore breastfeeding must be discontinued prior and during administration.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

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

Summary of the safety profile

Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Tabulated list of adverse reactions

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), not known (cannot be estimated from the available data)

Infections and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. reactivation of inactive chronic infection), sepsis, *Pneumocystis jirovecii* pneumonia, conjunctivitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: Lymphoma (see "description" below).

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders (see "description" below).
Not known: Eosinophilia

Immune system disorders
Rare: Allergic reactions, anaphylactic shock, hypogammaglobulinaemia.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes mellitus.

Psychiatric disorders
Uncommon: Depression, confusion.
Rare: Mood alterations.

Nervous system disorders
Common: Headache, tiredness, drowsiness.

Uncommon: Dizziness.
Very rare: Pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: Encephalopathy/leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Impaired vision, 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, not productive cough, short of breath and fever.
Rare: Pulmonary fibrosis, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain.
Common: Oral ulcers, diarrhoea.
Uncommon: Gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis.
Rare: Gingivitis.
Very rare: Haematemesis, haematorrhea, toxic megacolon.

Hepatobiliary disorders (see section 4.4)
Very common: Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.
Rare: Acute hepatitis.
Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitivity reactions, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare: Increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis.
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.
Not known: Skin exfoliation/dermatitis exfoliative.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.
Rare: Stress fracture.
Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders).

Renal and urinary disorders
Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.
Rare: Renal failure, oliguria, anuria, electrolyte disturbances.
Not known: Proteinuria.

Reproductive system and breast disorders
Uncommon: Inflammation and ulceration of the vagina.
Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

General disorders and administration site conditions

Rare: Fever, wound-healing impairment.
Not known: Asthenia, injection site necrosis, oedema.

Description of selected adverse reactions
The appearance and degree of severity of undesirable effects depends on the dose 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.

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.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy.

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

a) Symptoms of overdose
Toxicity of methotrexate mainly affects the haematopoietic system.

b) Treatment measures in the case of overdose
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 alkalisation 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: Other immunosuppressants
ATC code: L04AX03
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases.

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 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

Absorption
Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (doses between 7.5 mg/m^2 and 80 mg/m^2 body surface area), the mean bioavailability is approx. 70%, but considerable inter-individual and intra-individual deviations are possible (25–100%). Maximum serum concentrations are achieved after 1–2 hours.

Bioavailability of subcutaneous, intravenous and intramuscular injection is comparable and nearly 100%.

Distribution
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 cerebrospinal fluid 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 intra-hepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination
Excretion takes places, 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. There is pronounced enterohepatic circulation.

In the case of renal impairment, elimination is delayed significantly. Impaired elimination with regard to hepatic impairment 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*. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 25 °C. Do not freeze.
Keep the pre-filled pens in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled pens containing a colourless pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and embedded injection needle. The syringe is externally equipped with the device for self-administration (pen).

Metoject pre-filled pen is available as a three-step auto-injector that has a yellow cap and a yellow injection button or as a two-step auto-injector with a translucent protective cap and a blue needle cover.

Pack sizes:

Pre-filled pens containing 0.15 ml (7.5 mg), 0.2 ml (10 mg), 0.3 ml (15 mg), 0.4 ml (20 mg), 0.5 ml (25 mg) solution are available in packs of 1, 2, 4, 5, 6, 10, 11, 12, 14, 15, and 24 pre-filled pens.

The prefilled syringe within the pen may or may not have graduations on the barrel. These graduations are non-functional.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be 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 medicinal product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstrasse 6
22880 Wedel
Germany

8 MARKETING AUTHORISATION NUMBER

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