METOJECT 50 MG/ML S.C.

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Metoject 50 mg/ml S.C. solution for injection, pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg methotrexate.

1 pre-filled syringe of 0.15 ml contains 7.5 mg methotrexate.
1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.
1 pre-filled syringe of 0.55 ml contains 27.5 mg methotrexate.
1 pre-filled syringe of 0.60 ml contains 30 mg methotrexate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis:
Methotrexate can be used in the treatment of selected adults with severe rheumatoid arthritis, only when the diagnosis has been well established according to rheumatological standards, with inadequate response to other forms of antirheumatic therapy, including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Juvenile Idiopathic Arthritis:
Treatment of Polyarthritic forms of severe, active juvenile idiopathic arthritis in patients 3 years of age and above when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.

Psoriasis in adult patients:
Because of the high risk attending its use, Methotrexate is indicated only in the symptomatic control of severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established, as by biopsy and/or after dermatological consultation.

Crohn's Disease:
Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

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**.
The patient is to be explicitly informed about the fact of administration subcutaneously **once weekly**. 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).

Dosage 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. However, 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.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10-15 mg/m² body surface area (BSA)/**once weekly** administered subcutaneously. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m² body surface area/**once weekly**. However, an increased monitoring frequency is indicated if the dose is increased.
Patients with JIA should always be referred to a rheumatology specialist in the treatment of children/adolescents.

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)

Dosage in patients with psoriasis vulgaris and psoriatic arthritis
It is recommended that a test dose of 5 – 10 mg should be administered subcutaneously, 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.

Dosage in patients with Crohn's Disease
- Induction treatment:
  25 mg/week administered subcutaneously.
  Response to treatment can be expected after approximately 8 to 12 weeks.
- Maintenance treatment:
  15 mg/week administered subcutaneously.

There is not sufficient experience in the paediatric population to recommend Metoject 50 mg/ml for the treatment of Crohn's disease in this population.

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 µmol/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 should be given subcutaneously.

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 contraindicated in the case of
- hypersensitivity to methotrexate 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 and 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 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 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 (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 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: 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 is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and 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 and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

   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 section 4.5). 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).
4. Renal function should be monitored by renal function tests and urinalysis (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 medicinal products) or that 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 affection requires a quick diagnosis and discontinuation of methotrexate therapy. 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.

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.

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 are 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, yielding increased toxicity such as severe unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use 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 nonsteroidal 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.

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, azathioprine, cyclosporine).

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.

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 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy:
Metoject 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.

Breast-feeding:
Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, Metoject is contraindicated during breast-feeding (see section 4.3). Therefore breast-feeding must be discontinued prior to and throughout 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 (including reactivation of inactive chronic infection), sepsis, conjunctivitis.

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

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombocytopenia.
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 in the extremities, 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, *Pneumocystis carinii* pneumonia, 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: Photosensitisation, 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.

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.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following subcutaneous administration.
Not known: Asthenia, injection site necrosis.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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: Folic acid analogues
ATC code: L01BA01
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis. Immunomodulating and anti-inflammatory agent for the treatment of Crohn's disease.

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 psoriasis, psoriasis arthritis, chronic polyarthritis and Crohn's disease, 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.

International clinical guidelines reflect the use of methotrexate as a second choice for Crohn's disease patients that are intolerant or have failed to respond to first-line immunomodulating agents as azathioprine (AZA) or 6-mercaptopurine (6-MP).

The adverse events observed in the studies performed with methotrexate for Crohn's disease at cumulative doses have not shown a different safety profile of methotrexate than the profile it is already known. Therefore, similar cautions must be taken with the use of methotrexate for the treatment of Crohn's disease as in other rheumatic and non-rheumatic indications of methotrexate (see sections 4.4 and 4.6).

5.2 Pharmacokinetic properties

Absorption
Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70%, but considerable interindividual and intraindividual 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 intrahepatically. 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
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

The expiry date of the product is indicated on the packaging materials.

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 syringes of colourless glass (type I) of 1 ml capacity with embedded injection needle. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger

or

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with embedded injection needle. Plunger stoppers of chlorobutyl rubber (type I), polystyrene rods inserted on the stopper to form the syringe plunger and a patient safety built-in system to prevent needle stick injury and reuse of the needle.

Pack sizes:
Pre-filled syringes containing 7.5 mg/0.15 ml, 10 mg/0.20 ml, 12.5 mg/0.25 ml, 15 mg/0.30 ml, 17.5 mg/0.35 ml, 20 mg/0.40 ml, 22.5 mg/0.45 ml, 25 mg/0.50 ml, 27.5 mg/0.55 ml or 30 mg/0.6 ml solution are available in packs of 1, 4, 6, 12 and 24 syringes with embedded s.c. injection needle.
or

Pre-filled syringes containing 7.5 mg/0.15 ml, 10 mg/0.20 ml, 12.5 mg/0.25 ml, 15 mg/0.30 ml, 17.5 mg/0.35 ml, 20 mg/0.40 ml, 22.5 mg/0.45 ml, 25 mg/0.50 ml, 27.5 mg/0.55 ml or 30 mg/0.6 ml solution are available in packs of 1, 4, 6, 12 and 24 syringes with embedded s.c. injection needle with a patient safety built-in system.

All pack sizes are available with graduation marks.

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 healthcare 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.

Metoject may be marketed with a safety system to prevent needle stick injury and reuse of the needle.

Instructions for subcutaneous use of Metoject <u>without</u> patient safety built-in system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site.
2. Pull the protective plastic 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 syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.

Instructions for subcutaneous use of Metoject <u>with</u> patient safety built-in system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site.
2. Pull the protective plastic 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 syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.
7. A protective cover will automatically enclose the needle.

Note: The protection system that is triggered by the release of the protective cover can only be activated when the syringe has been emptied completely by pushing down the plunger as far as it goes.

7. MANUFACTURER

medac Gesellschaft für klinische Spezialpräparate mbH, Wedel, Germany.

8. MARKETING AUTHORISATION HOLDER

Tzamal Bio-Pharma, 20 Hamagshimim St.,Kiryat Matalon ,Petah-Tikva.

9. MARKETING AUTHORISATION NUMBER

145-34-33074-01/02/03/04

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