METOJECT®
Methotrexate

NAME OF THE MEDICINAL PRODUCT
Metoject 50 mg/ml solution for injection, pre-filled syringe.

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 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.

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

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

Posology and method of administration

Important warning about the dosage of Metoject (methotrexate)
In the treatment of rheumatoid arthritis, and psioriasis, 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.

Metoject should only be prescribed by physicians, with expertise in the use of methotrexate and full understanding of the risks of methotrexate therapy. The administration should routinely be done by healthcare professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the subcutaneous administration to the patient her/himself. 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 subcutaneously **once weekly.**
The patient is to be explicitly informed about the fact of administration **once a week**. 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 Pharmacokinetic properties and Special warnings and precautions for use).

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 patients with psoriasis vulgaris:
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.

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

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 contraindications.

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, ascitis)*:
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 Pharmacokinetic properties and Special warnings and precautions for use).

Method of administration:
The medicinal product is for single use only.
Metoject is given by subcutaneous route. (See section Special precautions for disposal and other handling).
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.

Contraindications
Metoject is contraindicated in the case of
1. hypersensitivity to the active substance or to any of the excipients listed in section List of excipients.
2. severe liver impairment (see section Posology and method of administration),
3. alcohol abuse,
4. severe renal impairment (creatinine clearance less than 30 ml/min, see section Posology and method of administration and Special warnings and precautions for use),
5. pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia,
6. serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
7. ulcers of the oral cavity and known active gastrointestinal ulcer disease,
8. pregnancy and breast-feeding (see section Fertility, pregnancy and lactation)
9. concurrent vaccination with live vaccines.

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.
The test 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 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 co 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 patients'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 section Contraindications and Interaction with other medical product and other forms of interaction). 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 urinalysis (see sections Posology and method of administration and Contraindication).
   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 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 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 individuals taking methotrexate (see section Undesirable effect). 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 Pharmacokinetic properties).

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 Fertility, pregnancy and lactation). 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 Fertility, Pregnancy, and Lactation.

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

Pediatric population
Use in patients below 18 years of age is not recommended as insufficient data on efficacy and safety is available for this population.

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 Special warnings and precautions for use). Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, 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 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, sulfonamides, diphenylhydantoins, (phenytoin) 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 (e.g. 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 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. sulfonamides, trimethoprim-sulfamethoxazole, 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, azathioprin).

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.

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 Special warnings and precautions for use). 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. 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 Preclinical safety data). 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 Contraindications).
Therefore breast-feeding 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.

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.

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, anemia, 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 organize 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)

Infection and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. 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, anemia, 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/ 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, *Pneumocystis jirovecii* 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 Special warnings and precautions for use)
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 reaction, 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.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.

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 authorization 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 pharmacovigilance@dipa.co.id

Overdose

a) Symptoms of overdose
   Toxicity of methotrexate mainly affects the hematopoietic system.
b) Treatment measures in the case of overdose
   Calcium folinate is the specific antidote for neutralizing 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 alkalization 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Other immunosuppressants, ATC code: L04AX03
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases.

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, 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.

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 injection is 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 metabolized 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.

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.

PHARMACEUTICAL PARTICULARS
List of excipients
Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

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

Shelf-life
2 years.

Special precautions for storage
Store below 25°C. Keep the pre-filled syringes in the outer carton in order to protect from light.
Nature and contents of container
Nature of container:
Pre-filled syringes of colourless glass (type I) of 1 ml capacity with embedded injection needle, packed in blisters. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger

Pack sizes:
Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of syringes with embedded s.c. injection needle.

All pack sizes are available with graduation marks.

Not all pack sizes may be marketed.

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.

Instructions for subcutaneous use
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area of and around the chosen injection site with soap and water or disinfectant.
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.

HARUS DENGAN RESEP DOKTER

PACKAGING AND REGISTRATION NUMBER
METOJECT, Box, 1 pre-filled syringe @ 0.15 ml, Reg. No.: DKI2030600643A1
METOJECT, Box, 1 pre-filled syringe @ 0.20 ml, Reg. No.: DKI2030600643A1
METOJECT, Box, 1 pre-filled syringe @ 0.30 ml, Reg. No.: DKI2030600643A1
METOJECT, Box, 1 pre-filled syringe @ 0.40 ml, Reg. No.: DKI2030600643A1

MANUFACTURED BY:
Oncotec Pharma Produktion GmbH
Am Pharmapark, Dessau-Rosslau, Germany
released by medac GmbH
Theaterstraße 6, D-22880 Wedel, Germany

IMPORTED BY:
PT Dipa Pharmalab Intersains
Majalengka – Indonesia

Date of revision: 2026-02-24

Leaflet: Informasi untuk pasien

METOJECT®

Metotreksat 50 mg/ml

cairan injeksi, *pre-filled syringe*

Bacalah leaflet ini dengan cermat sebelum Anda memulai untuk menggunakan obat ini karena leaflet ini memuat informasi penting untuk Anda.

- Simpan leaflet ini. Anda mungkin akan membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Hal itu dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, beri tahu dokter Anda atau apoteker. Ini termasuk kemungkinan efek samping yang tidak tercantum pada leaflet ini. Lihat pada bagian ke-4.

Apa yang tercantum dalam leaflet ini?

1. Isi dan Indikasi Metoject

Metoject mengandung metotreksat sebagai zat aktif.
Metotreksat memiliki sifat-sifat sebagai berikut:

- mengganggu pertumbuhan sel-sel tertentu dalam tubuh yang bereproduksi secara cepat
- mengurangi aktivitas sistem imun (mekanisme pertahanan tubuh)
- memiliki efek anti inflamasi

Metoject diindikasikan untuk pengobatan:

- Artritis reumatoid aktif pada pasien dewasa.
- *Severe recalcitrant disabling psoriasis* (psoriasis rekalsitran berat) yang tidak cukup responsif terhadap terapi bentuk lainnya, seperti fototerapi, PUVA, dan retinoid.

Artritis Reumatoid (AR) merupakan penyakit kolagen kronis, ditandai dengan peradangan pada membran sinovial (membran sendi). Membran ini memproduksi suatu cairan yang berfungsi sebagai lubrikan untuk banyak sendi. Inflamasi yang terjadi menyebabkan penebalan pada membran dan pembengkakan pada sendi.

Psoriasis merupakan penyakit kulit kronis yang umum, ditandai dengan bercak merah yang tertutup oleh sisik tebal, kering, keperakan, dan melekat.

Metoject memodifikasi dan memperlambat perkembangan penyakit.

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2. Hal yang perlu Anda ketahui sebelum menggunakan Metoject

Jangan gunakan Metoject:

- jika Anda alergi terhadap metotreksat atau komposisi lain dari obat ini (tercantum pada bagian ke-6),
- jika Anda menderita penyakit hati atau ginjal yang parah atau penyakit darah,
- jika Anda sering mengonsumsi alkohol dalam jumlah yang banyak,
- jika Anda menderita infeksi berat, seperti tuberkulosis, HIV, atau sindrom imunodefisiensi lainnya,
- jika Anda menderita ulkus pada mulut, ulkus lambung, atau ulkus pencernaan,
- jika Anda sedang hamil atau menyusui (lihat bagian Kehamilan, menyusui, dan fertilitas),
- jika Anda mendapatkan vaksinasi dengan vaksin hidup pada waktu yang bersamaan.

Peringatan dan pencegahan

Bicarakan dengan dokter Anda atau apoteker sebelum menggunakan Metoject jika:

- Anda merupakan lansia atau jika Anda merasa tidak dalam kondisi baik, atau lemah,
- fungsi hati Anda terganggu,
- Anda menderita dehidrasi (kehilangan cairan).
- Anda menderita diabetes melitus dan sedang menggunakan insulin

Perhatian khusus untuk pengobatan dengan Metoject

Metotreksat memengaruhi produksi sperma dan sel telur, yang bersifat reversibel pada sebagian besar kasus. Metotreksat dapat menyebabkan keguguran dan cacat lahir. Pada pasien wanita harus menunda kehamilan selama penggunaan metotreksat hingga minimal 6 bulan setelah terapi dihentikan. Sedangkan pada pasien laki-laki setidaknya 3 bulan setelah terapi dihentikan. Lihat juga bagian "Kehamilan, menyusui dan fertilitas".

Pemeriksaan tindak lanjut dan tindakan pencegahan yang direkomendasikan

Efek samping berat dapat terjadi pada penggunaan Metoject, bahkan pada dosis rendah. Untuk mendeteksi efek samping tersebut sesegera mungkin, maka harus dilakukan pemeriksaan dan tes laboratorium oleh dokter Anda.

Sebelum memulai pengobatan

Sebelum Anda memulai pengobatan, sampel darah Anda akan diambil untuk memastikan bahwa Anda memiliki jumlah sel darah yang cukup. Akan dilakukan pemeriksaan darah untuk menilai fungsi liver (hati) dan untuk mengetahui apakah Anda menderita hepatitis. Selanjutnya akan dilakukan pemeriksaan albumin serum (protein di dalam darah), hepatitis (infeksi hati) dan fungsi ginjal Anda. Dokter mungkin juga memutuskan untuk menjalankan tes hati lainnya, beberapa di antaranya mungkin berupa gambar hati Anda dan yang lainnya mungkin memerlukan sampel kecil jaringan yang diambil dari hati untuk memeriksanya lebih dekat. Dokter Anda mungkin juga melakukan pemeriksaan apakah Anda menderita tuberkolosis dan akan melakukan pemeriksaan X-ray dada atau fungsi paru.

Selama pengobatan

Dokter Anda mungkin akan melakukan pemeriksaan berikut ini:

- Pemeriksaan rongga mulut dan faring untuk melihat adanya perubahan pada mukosa seperti peradangan atau ulserasi.

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- Tes darah / menghitung jumlah sel darah dan pengukuran kadar metotreksat pada serum
- Tes darah untuk memantau fungsi hati.
- Rontgen untuk memantau fungsi hati
- Memeriksa sampel jaringan hati
- Tes darah untuk memantau fungsi ginjal
- Pemeriksaan sistem saluran pernapasan dan bila perlu pemeriksaan fungsi paru

Sangat penting untuk Anda membuat jadwal pemeriksaan ini.
Jika hasil dari salah satu pemeriksaan tersebut memberikan hasil positif, dokter Anda akan menyesuaikan pengobatannya.

Pasien lanjut usia
Pada pasien lanjut usia yang sedang menjalani perawatan dengan metotreksat harus diawasi oleh dokter agar efek sampingnya dapat diketahui sedini mungkin.
Gangguan fungsi hati dan ginjal yang berkaitan dengan usia serta rendahnya cadangan asam folat dalam tubuh di usia lanjut maka memerlukan dosis metotreksat yang relatif rendah.

Tindakan pencegahan lain
Perdarahan akut dari paru-paru telah dilaporkan pada pasien yang mengalami penyakit reumatologis dengan pengobatan metotreksat. Jika terdapat darah pada air liur atau Anda mengalami batuk darah, Anda harus segera menghubungi dokter Anda.

Metotreksat dapat memengaruhi sistem imun dan hasil vaksinasi. Metotreksat juga dapat memengaruhi hasil pemeriksaan imunologi. Infeksi kronis (misalnya herpes zoster [*shingles*], tuberkulosis, hepatitis B, atau C) yang tidak aktif, dapat timbul. Selama pengobatan dengan Metoject Anda tidak boleh divaksinasi dengan vaksin aktif.

Pemakaian metotreksat dapat membuat kulit lebih sensitif terhadap sinar matahari Hindari sinar matahari terik, tempat tidur panas atau lampu pemanas yang bukan alat kesehatan. Untuk melindungi kulit Anda dari sinar matahari, gunakan pakaian yang sesuai atau gunakan tabir surya dengan SPF tinggi.

Dermatitis yang diinduksi oleh radiasi dan kulit yang terbakar sinar matahari dapat muncul kembali saat pengobatan dengan metotreksat *(recall-reaction)*.
Lesi psoriatik dapat bertambah buruk selama radiasi sinar UV dan pemberian metotreksat secara simultan.
Pembesaran kelenjar getah bening (limfoma) dapat terjadi dan pengobatan harus dihentikan.

Diare dapat menjadi efek toksik dari Metoject dan pengobatan harus dihentikan. Jika Anda mengalami diare, segera konsultasikan dengan dokter Anda.

Gangguan otak tertentu *(encephalopathy/leukoencephalopathy)* telah dilaporkan terjadi pada pasien kanker yang menerima metotreksat. Efek samping ini tidak dapat dikecualikan ketika metotreksat digunakan untuk mengobati penyakit lain.

Jika Anda, pasangan atau teman, baru saja mengalami atau memburuknya gejala neurologis termasuk lemah otot, gangguan penglihatan, berubah pikiran, hilang ingatan dan hilang arah yang dapat menyebabkan kebingungan dan perubahan kepribadian, segera hubungi dokter Anda karena hal ini mungkin terjadi gejala infeksi otak yang sangat jarang dan serius yang disebut Progressive Multifocal Leukoncephalopathy (PML).

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Obat lain dan Metoject
Konsultasikan kepada dokter Anda atau apoteker jika Anda sedang mengonsumsi, baru-baru ini mengonsumsi, atau akan mengonsumsi obat lain. Perlu diperhatikan bahwa hal ini juga berlaku untuk obat-obatan lain yang akan Anda konsumsi di waktu yang akan datang.

Efek dari pengobatan mungkin terpengaruh jika Metoject diberikan bersamaan dengan obat-obatan berikut ini:

- **Antibiotik** seperti: tetrasiklin, kloramfenikol, dan antibiotik spektrum luas *non-absorbable*, penisilin, glikopeptida, sulfonamida, siprofloksasin, dan sefalotin (obat-obatan untuk mencegah/mengobati infeksi tertentu).
- **Obat anti inflamasi non steroid (OAINS)** atau **salisilat** (obat penghilang rasa nyeri dan/atau peradangan seperti asam asetilsalisilat, diklofenak dan ibuprofen atau pirazol).
- **Metamizol** (sinonim dengan novainsulfon dan dipiron) obat untuk mengatasi rasa sakit yang parah dan/atau demam
- **Probenesid** (obat untuk asam urat).
- Asam organik lemah seperti *loop* ***diuretic*** *("water tablet").*
- Obat-obatan yang memiliki efek samping pada **sumsum tulang**, misalnya trimetoprim-sulfametoksazol (antibiotik) dan pirimetamin.
- **Obat-obatan lain yang digunakan untuk pengobatan artritis reumatoid** seperti leflunomida, sulfasalazin, dan azatioprin.
- Siklosporin (untuk menekan sistem kekebalan tubuh)
- Merkaptopurin (obat-obatan **sitostatik**).
- Retinoid (obat-obatan untuk **psoriasis** dan penyakit dermatologis lainnya).
- Teofilin (obat-obatan untuk **asma bronkial** dan penyakit paru lainnya).
- Beberapa obat untuk **masalah lambung** seperti omeprazol dan pantoprazol.
- Hipoglikemik (obat-obatan yang digunakan untuk **menurunkan gula darah**).

Vitamin yang mengandung **asam folat** dapat mengurangi efek pengobatan dan hanya dikonsumsi atas saran dari dokter Anda.

Vaksinasi dengan vaksin hidup harus dihindari.

Metoject dengan makanan, minuman, dan alkohol
Alkohol, kopi dalam jumlah banyak, minuman ringan yang mengandung kafein dan teh hitam harus dihindari selama pengobatan dengan Metoject.

Kehamilan, menyusui, dan fertilitas

Kehamilan
Jangan menggunakan Metoject selama masa kehamilan atau jika Anda berencana untuk hamil. Metotreksat dapat menyebabkan cacat lahir, membahayakan bayi dalam kandungan atau menyebabkan keguguran. Penggunaan obat ini berhubungan dengan terjadinya malformasi (kelainan bentuk) tengkorak, wajah, jantung dan pembuluh darah, otak, dan anggota gerak. Oleh karena itu, metotreksat tidak dapat diberikan kepada pasien yang sedang hamil atau berencana untuk hamil. Kemungkinan hamil pada wanita usia subur harus disingkirkan dengan pengukuran yang tepat, seperti tes kehamilan sebelum memulai pengobatan. Anda harus menghindari kehamilan selama mengonsumsi metotreksat dan setidaknya selama 6 bulan setelah pengobatan dihentikan dengan menggunakan kontrasepsi

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yang efektif untuk jangka waktu tersebut (lihat juga bagian "Peringatan dan tindakan pencegahan").
Jika Anda sedang hamil atau kemungkinan dalam keadaan hamil selama masa pengobatan, bicarakan dengan dokter Anda sesegera mungkin. Anda harus mendapatkan saran mengenai risiko terjadinya efek membahayakan pada anak dari proses pengobatan yang dilakukan.
Jika Anda berencana untuk hamil, konsultasikan kepada dokter Anda. Dokter Anda dapat merujuk Anda kepada dokter spesialis terkait sebelum memulai pengobatan.

Menyusui
Hentikan proses menyusui sebelum dan selama menjalani pengobatan dengan Metoject.

Fertilitas pada pria
Bukti yang tersedia tidak menunjukkan peningkatan risiko malformasi atau keguguran jika ayah mengonsumsi metotreksat kurang dari 30 mg/minggu, namun risiko tersebut tidak dapat sepenuhnya disingkirkan. Metotreksat dapat bersifat genotoksik. Hal ini berarti bahwa obat tersebut dapat menyebabkan mutasi genetik. Metotreksat dapat memengaruhi produksi sperma dengan potensi menyebabkan cacat lahir. Oleh karena itu, Anda harus menghindari untuk memiliki anak atau menyumbangkan sel sperma saat mengonsumsi metotreksat dan setidaknya selama 3 bulan setelah pengobatan dihentikan.

Mengemudi dan menggunakan mesin
Pengobatan dengan Metoject dapat menyebabkan efek samping yang memengaruhi sistem saraf pusat, seperti kelelahan dan pusing. Dengan demikian kemampuan untuk mengendarai kendaraan dan/ atau mengoperasikan mesin, dalam kasus-kasus tertentu, dapat membahayakan. Jika Anda merasa lelah atau mengantuk, Anda tidak boleh mengemudi atau menggunakan mesin.

Metoject mengadung sodium
Obat ini mengandung sodium tidak kurang dari 1 mmol (23 mg) per dosis maksudnya "bebas sodium".

3. Cara Penggunaan Metoject

Peringatan penting mengenai dosis Metoject (metotreksat).
Untuk pengobatan artritis reumatoid dan psoriasis gunakan Metoject hanya **satu kali dalam seminggu**. Penggunaan Metoject (metotreksat) terlalu banyak dapat berakibat fatal. Harap dibaca dengan hati-hati pada bagian 3 pada leaflet ini. Jika ada pertanyakan, tanyakan dokter dan apoter Anda sebelum menggunakan obat ini.

Selalu gunakan obat ini sesuai dengan saran dokter Anda. Tanyakan kepada dokter Anda atau apoteker jika Anda tidak yakin.

Dokter Anda akan menentukan dosis untuk Anda, yang ditentukan secara individual. Biasanya efek dari pengobatan akan muncul dalam waktu 4 – 8 minggu.

Metoject diberikan di bawah pengawasan dokter atau staf perawat kesehatan melalui injeksi di bawah kulit (injeksi subkutan) yang diberikan **seminggu sekali saja**. Diskusikan dengan dokter Anda hari yang sesuai tiap minggunya untuk injeksi.

Metode dan durasi pemberian
Metoject injeksi subkutan yang diberikan **seminggu sekali**!

Durasi pengobatan ditentukan oleh dokter yang merawat. Pengobatan artritis rheumatoid dan psoriasis vulgaris dengan Metoject merupakan pengobatan jangka panjang.

Pada awal pengobatan, Metoject dapat diinjeksikan oleh tenaga medis. Namun dokter Anda mungkin akan memutuskan untuk Anda bisa belajar bagaimana menyuntikkan tepat di bawah kulit sendiri, kecuali Anda telah terlatih akan melakukannya.

Dengan alasan apapun, Anda tidak diperbolehkan untuk menyuntikkan Metoject sendiri, sebelum Anda menerima pelatihan.
Silakan lihat petunjuk penggunaan pada bagian akhir leaflet.

Cara penanganan dan pembuangan sisa produk harus disesuaikan dengan sediaan sitostatik lainnya sesuai dengan persyaratan setempat. Petugas kesehatan yang sedang hamil sebaiknya tidak menangani dan/atau menyuntikkan Metoject.

Metotreksat tidak boleh mengenai permukaan kulit atau mukosa. Jika terjadi kontaminasi, area yang terkena harus segera dibilas dengan air mengalir dalam jumlah yang banyak.

Jika Anda menggunakan Metoject lebih banyak dari yang seharusnya
Jika Anda menggunakan Metoject dengan jumlah yang lebih banyak dari yang seharusnya, segera konsultasikan dengan dokter Anda.

Jika Anda lupa untuk menggunakan Metoject
Jangan menggunakan dosis secara ganda untuk menggantikan dosis yang terlupakan.

Jika Anda berhenti menggunakan Metoject
Jika Anda berhenti menggunakan Metoject, segera konsultasikan dengan dokter Anda.

Jika Anda merasakan bahwa efek Metoject yang digunakan terlalu kuat atau terlalu lemah, konsultasikan dengan dokter Anda atau apoteker.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, obat ini dapat menyebabkan efek samping, walaupun tidak setiap orang mengalaminya.
Frekuensi serta tingkat keparahan efek samping tergantung dari tingkat dosis dan frekuensi pemberian. Karena efek samping yang parah juga dapat terjadi pada dosis rendah, maka penting agar Anda dipantau secara rutin oleh dokter Anda. Dokter Anda akan melakukan **tes untuk memeriksa kelainan** yang berkembang di dalam darah (seperti sel darah putih rendah, trombosit rendah, dan limfoma) dan perubahan pada ginjal dan hati.

Segera konsultasikan dengan dokter Anda jika Anda mengalami salah satu gejala di bawah ini, karena dapat mengindikasikan sesuatu yang serius, efek samping yang berpotensi mengancam nyawa, yang memerlukan pengobatan spesifik mendesak.

- **batuk kering, batuk *non-productive*, sesak nafas dan demam,** hal tersebut bisa jadi merupakan tanda-tanda peradangan pada paru [umum]

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- **meludah atau batuk darah**; hal ini dapat menjadi tanda perdarahan dari paru [tidak diketahui]
- **gejala kerusakan hati seperti kulit menguning dan bagian putih pada mata;** metotreksat dapat menyebabkan kerusakan hati kronis (sirosis hati), pembentukan jaringan parut di hati (fibrosis hati), degenerasi lemak pada hati [semua tidak umum], peradangan pada hati (hepatitis akut) [jarang] dan gagal hati [sangat jarang]
- **gejala alergi seperti ruam kulit termasuk kulit gatal kemerahan, pembengkakan pada tangan, kaki, pergelangan kaki, wajah, bibir, mulut atau tenggorokan (yang dapat menyebabkan kesulitan menelan atau bernapas) dan merasa seperti Anda akan pingsan;** hal ini mungkin merupakan tanda-tanda reaksi alergi yang parah atau syok anafilaksis [jarang]
- **gejala kerusakan ginjal seperti pembengkakan tangan, pergelangan kaki atau kaki atau perubahan frekuensi buang air kecil berupa penurunan (oliguria) atau tidak adanya urin (anuria)**; ini mungkin merupakan tanda gagal ginjal [jarang]
- **gejala infeksi, misalnya demam, menggigil, terasa sakit *(achiness)*, sakit tenggorokan**; metotreksat dapat membuat Anda lebih rentan terhadap infeksi. Infeksi berat seperti jenis pneumonia tertentu (*Pneumocystis carinii pneumonia*) atau keracunan darah (sepsis) dapat terjadi [jarang]
- **gejala seperti kelemahan pada salah satu sisi tubuh (*stroke*) atau nyeri, bengkak, kemerahan dan rasa hangat yang tidak biasa di salah satu kaki Anda (trombosis vena dalam); Ini mungkin terjadi ketika gumpalan darah yang terlepas menyebabkan penyumbatan pada pembuluh darah** (peristiwa tromboembolik) [jarang]
- **demam dan kemunduran serius pada kondisi Anda secara umum, atau demam mendadak disertai dengan sakit tenggorokan atau mulut, atau masalah buang air kecil**; metotreksat dapat menyebabkan penurunan drastis pada sel darah putih tertentu (agranulositosis) dan supresi sumsum tulang yang parah [sangat jarang]
- perdarahan **yang tidak terduga, misalnya gusi berdarah, darah dalam urin, muntah darah atau memar**, ini bisa menjadi tanda-tanda penurunan sejumlah besar trombosit darah yang parah yang disebabkan oleh depresi sumsum tulang yang parah [sangat jarang]
- **gejala seperti sakit kepala hebat yang sering kali dikombinasikan dengan demam, kekakuan leher, perasaan mual, muntah, disorientasi dan sensitivitas terhadap cahaya** dapat mengindikasikan peradangan pada selaput otak (meningitis aseptik akut) [sangat jarang]
- gangguan otak tertentu (ensefalopati/leukoensefalopati) telah dilaporkan pada pasien kanker yang menerima metotreksat. Efek samping ini tidak dapat dikecualikan ketika terapi metotreksat digunakan untuk mengobati penyakit lain. Tanda-tanda gangguan otak semacam ini dapat **mengubah keadaan mental, gangguan gerak (ataksia), gangguan penglihatan atau gangguan memori** [tidak diketahui]
- **ruam kulit yang parah atau kulit melepuh (ini juga dapat terjadi pada mulut, mata, dan organ genital Anda**); hal ini mungkin merupakan tanda-tanda kondisi yang disebut sindrom Stevens-Johnson atau sindrom kulit terbakar (Nekrolisis Epidermal Toksik (NET) / sindrom Lyell's) [sangat jarang]

Berikut ini merupakan efek samping lain yang dapat terjadi:

Sangat umum: dapat terjadi pada lebih dari 1 dari 10 orang

- Peradangan pada lapisan mulut, gangguan pencernaan, nyeri, kehilangan nafsu makan, sakit pada bagian perut.

- Tes pada fungsi hati yang tidak normal (ASAT, ALAT, bilirubin, alkalin fosfatase).

Umum: dapat terjadi pada 1 dari 10 orang
- Ulkus mulut, diare.
- Ruam, kemerahan pada kulit, gatal.
- Sakit kepala, kelelahan, mengantuk.
- Penurunan pembentukan sel darah dengan penurunan sel darah putih dan/atau merah dan/atau trombosit.

Tidak umum: dapat terjadi pada 1 dari 100 orang
- Peradangan tenggorokan.
- Radang usus, muntah, radang pankreas, tinja berwarna hitam atau gelap, ulkus dan perdarahan gastrointestinal
- Reaksi seperti terbakar matahari akibat meningkatnya sensitivitas kulit terhadap cahaya, rambut rontok, peningkatan jumlah nodul rematik, ulkus kulit, *shingles*/herpes zoster, radang pembuluh darah, ruam kulit seperti herpes, gatal-gatal.
- Onset diabetes mellitus
- Pusing, kebingungan, depresi.
- Penurunan serum albumin.
- Penurunan jumlah semua sel darah dan trombosit.
- Peradangan dan ulkus pada kandung kemih atau vagina, penurunan pada fungsi ginjal, gangguan saat buang air kecil.
- Nyeri sendi, nyeri otot, penurunan massa tulang.

Jarang: dapat terjadi pada 1 dari 1.000 orang
- Peradangan pada jaringan gusi
- Peningkatan pigmentasi kulit, jerawat, bintik-bintik biru pada kulit karena perdarahan pembuluh darah (ekimosis, petekie), peradangan alergi pada pembuluh darah.
- Penurunan jumlah antibodi dalam darah.
- Infeksi (termasuk reaktivasi infeksi kronis yang tidak aktif), mata merah (konjungtivitis).
- Perubahan emosi (perubahan suasana hati).
- Gangguan penglihatan.
- Peradangan kantung di sekitar jantung, akumulasi cairan di dalam kantung di sekitar jantung, gangguan pada proses pengisian jantung karena akumulasi cairan di dalam kantung di sekitar jantung.
- Tekanan darah rendah.
- Pembentukan jaringan parut di paru (fibrosis paru), sesak nafas dan asma bronkial, akumulasi cairan dalam kantung di sekitar paru.
- Fraktur yang parah.
- Gangguan elektrolit.
- Demam, gangguan penyembuhan luka.

Sangat jarang: dapat terjadi pada 1 dari 10.000 orang
- Dilatasi toksik akut pada usus (megakolon toksik).
- Peningkatan pigmentasi kuku, radang kutikula (paronikia akut), infeksi folikel rambut yang parah (furunkulosis), pembesaran pembuluh darah kecil yang terlihat.
- Kerusakan lokal (pembentukan abses steril, perubahan pada jaringan lemak) pada tempat penyuntikan .

- Nyeri, hilangnya kekuatan atau sensasi mati rasa atau kesemutan / memiliki kepekaan yang lebih rendah terhadap rangsangan dibandingkan dengan orang normal, perubahan rasa pada pengecap (sensasi rasa logam), kejang, kelumpuhan, meningitis.
- Gangguan penglihatan, gangguan mata non-inflamasi (retinopati).
- Hilangnya dorongan seksual, impotensi, pembesaran payudara pria, pembentukan sperma yang rusak (oligospermia), gangguan menstruasi, keputihan.
- Pembesaran kelenjar getah bening (limfoma).
- Kelainan limfoproliferatif (pertumbuhan sel darah putih yang berlebihan)

Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia
- Peningkatan jumlah sel darah putih tertentu.
- Mimisan.
- Protein dalam urin.
- Merasa lemah.
- Kerusakan tulang pada rahang (sekunder akibat pertumbuhan berlebihan sel darah putih)
- Kerusakan jaringan pada tempat penyuntikan
- Kemerahan dan pengelupasan kulit
- Pembengkakan

Pemberian metotreksat secara subkutan dapat ditoleransi dengan baik secara lokal. Hanya reaksi lokal ringan pada kulit yang teramati, dan akan membaik selama terapi.

Pelaporan efek samping
Jika Anda mengalami efek samping, konsultasikan dengan dokter Anda atau apoteker. Hal ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Anda juga dapat melaporkan efek samping secara langsung melalui pharmacovigilance@dipa.co.id. Dengan melaporkan efek samping secara langsung, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan Metoject

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Simpan pada suhu di bawah 25^0C.
Simpan *pre-filled syringe* pada kemasan karton untuk melindungi dari cahaya.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada kemasan. Tanggal kedaluwarsa mengacu pada hari terakhir di bulan tersebut.

Jangan membuang obat apapun melalui saluran air limbah atau saluran limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu menjaga lingkungan.

6. Isi dalam kemasan dan informasi lainnya

Kandungan Metoject
- Zat aktif Metoject adalah metotreksat
- Bahan lainnya adalah natrium klorida, natrium hidroksida, *air/larutan untuk injeksi*.

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Pemerian Metoject dan isi dalam kemasan
Metoject *pre-filled syringe* mengandung larutan kuning kecoklatan jernih.

Besar kemasan yang tersedia:
Pre-filled syringe dengan jarum suntik untuk penggunaan subkutan yang berisi 0,15 ml, 0,20 ml, 0,25 ml, 0,30 ml, 0,35 ml, 0,40 ml, 0,45 ml, 0,50 ml, 0,55 ml, dan 0,60 ml cairan injeksi dalam kemasan berisi 1 *pre-filled syringe* dan dikemas dalam blister.

Tidak semua kemasan dipasarkan.

HARUS DENGAN RESEP DOKTER

KEMASAN DAN NOMOR IZIN EDAR
METOJECT, Dus, 1 *pre-filled syringe* @ 0,15 ml, No. Reg.: DKI2030600643A1
METOJECT, Dus, 1 *pre-filled syringe* @ 0,20 ml, No. Reg.: DKI2030600643A1
METOJECT, Dus, 1 *pre-filled syringe* @ 0,30 ml, No. Reg.: DKI2030600643A1
METOJECT, Dus, 1 *pre-filled syringe* @ 0,40 ml, No. Reg.: DKI2030600643A1

DIPRODUKSI OLEH:
Oncotec Pharma Produktion GmbH
Am Pharmapark, Dessau-Rosslau, Jerman
dirilis oleh medac GmbH
Theaterstraβe 6, D-22880 Wedel, Jerman

DIIMPOR OLEH:
PT Dipa Pharmalab Intersains
Majalengka – Indonesia

Revisi terakhir brosur ini 2026-02-24

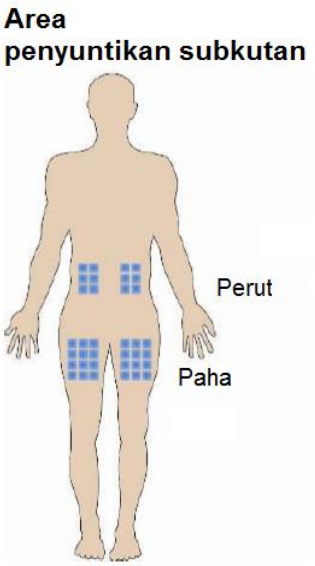
Petunjuk penggunaan untuk subkutan

Metoject sebagai injeksi di bawah kulit yang diberikan hanya satu kali seminggu. Baca dengan cermat petunjuk di bawah ini sebelum memulai injeksi, dan selalu gunakan teknik injeksi yang disarankan oleh dokter, apoteker, atau perawat Anda.

Jika ada masalah atau pertanyaan, hubungi dokter, apoteker, atau perawat Anda.

Persiapan
Pilih tempat yang bersih, cukup terang, dan rata.
Cuci tangan Anda dengan hati-hati.
Buka kemasan metotreksat *pre-filled syringe* dan bacalah leaflet dengan saksama. Keluarkan *pre-filled syringe* dari kemasan pada suhu kamar.
Sebelum digunakan, periksa syringe Metoject untuk mengecek adanya cacat visual (retakan). Jika gelembung udara kecil terlihat dalam larutan, hal ini tidak akan memengaruhi dosis ataupun membahayakan Anda.

Lokasi penyuntikan



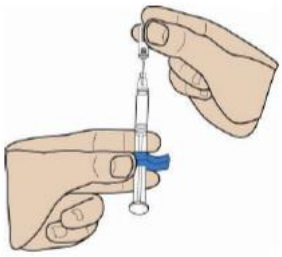
Lokasi terbaik untuk melakukan injeksi adalah:
– paha atas
– perut kecuali di sekitar pusar

- Jika seseorang membantu Anda untuk menyuntikkan, maka dia dapat memberikan suntikan tersebut pada bagian belakang lengan Anda, tepat di bawah bahu.
- Ubah lokasi injeksi untuk masing-masing suntikan yang diberikan. Hal ini dapat mengurangi risiko terjadinya iritasi pada lokasi injeksi.
- Jangan menyuntikkan pada area kulit yang lunak, memar, merah, keras, bekas luka, atau lokasi di mana Anda memiliki *stretch mark*. Jika Anda menderita psoriasis, Anda tidak boleh mencoba untuk menyuntikkan di bagian kulit yang menonjol, tebal, merah atau bersisik, dan di daerah bercak atau lesi.

Injeksi larutan

1. Pilih lokasi penyuntikan dan bersihkan area sekeliling tempat penyuntikan dengan sabun dan air atau disinfeksi.

2. Lepaskan tutup plastik pelindung



Lepaskan tutup plastik pelindung berwarna abu-abu dengan hati-hati dengan cara menarik secara langsung dari syringe. Jika tutup sangat kaku, putar sedikit dengan gerakan menarik.
Penting: **Jangan** menyentuh jarum dari pre-filled syringe.
Catatan: Setelah Anda lepaskan tutupnya, segera lakukan penyuntikan.

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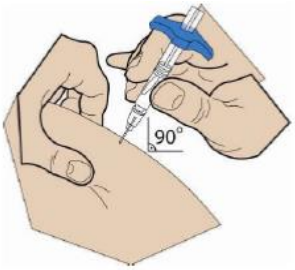
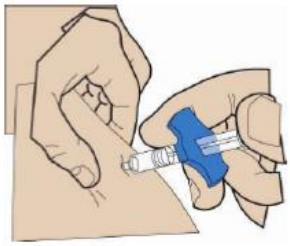
3. Memasukkan jarum



Dengan menggunakan dua jari, cubit kulit dan masukkan jarum ke dalam kulit dengan cepat pada sudut 90^0C.

4. Injeksi



Masukkan jarum sepenuhnya ke dalam lipatan kulit.
Dorong *plunger* ke bawah secara perlahan dan masukkan cairan ke dalam kulit Anda. Pegang kulit sampai proses injeksi selesai.
Tarik jarum suntik dengan hati-hati.

5. Buang jarum suntik bekas pakai beserta jarumnya ke tempat sampah khusus benda tajam. Jangan buang ke tempat sampah rumah tangga.

Metotreksat tidak boleh bersentuhan dengan permukaan kulit atau mukosa. Jika terjadi harus segera dibilas dengan air mengalir dalam jumlah banyak.

Jika Anda atau seseorang di sekitar Anda terluka oleh jarum, segera konsultasikan dengan dokter Anda dan jangan gunakan *pre-filled syringe* tersebut.

Cara pembuangan dan penanganan lainnya
Cara penanganan dan pembuangan obat dan *pre-filled syringe* harus disesuaikan dengan persyaratan setempat. Petugas kesehatan yang hamil sebaiknya tidak menangani dan/atau mengadministrasikan Metoject.

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