SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zlatal 17.5 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 25 mg methotrexate (as methotrexate disodium).

1 pre-filled syringe of 0.7 ml contains 17.5 mg methotrexate.

Contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, yellow solution with a pH of 8.0 - 9.0 and an osmolality of approximately 300 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zlatal is indicated for the treatment of

-active rheumatoid arthritis in adult patients,

-polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti- inflammatory drugs (NSAIDs) has been inadequate,

-severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

- 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

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Zlatal should be performed under direct medical supervision.

Important warning about the dosage of Zlatal (methotrexate)
In the treatment of rheumatoid arthritis, active juvenile idiopathic arthritis, psoriasis, psoriatic arthritis and Crohn's disease requiring dosing once a week. Zlatal (methotrexate) **must only be used once a week**. Dosage errors in the use of Zlatal (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Posology

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 patient tolerability, the initial dose may be increased. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression**.** Response to treatment can be expected after approximately 4 – 8 weeks. Once the desired therapeutic result has been achieved, 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)/week. In therapy-refractory cases the weekly dose may be increased up to 20mg/m² body surface area/week. However, an increased monitoring frequency is indicated if the dose is increased.

Parenteral administration is limited to subcutaneous injection.

Patients with JIA should always be referred to a rheumatology unit specializing in the treatment of children/adolescents.

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

Dosage in patients with psoriasis vulgaris and psoriatic arthritis:

It is recommended that a test dose of 5 - 10 mg be parenterally administered one week prior to initiation of therapy, in order to detect idiosyncratic adverse effects. The recommended initial dose is 7.5 mg 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. Once the desired therapeutic result has been achieved, 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.

Dosage in adult 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.

This product is not indicated for paediatric patients with Crohn’s disease (see section 4.1).

Patients with renal impairment:

Methotrexate 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	Zlatal 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 when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/L)

For a 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 patient 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 5.2 and 4.4).

Duration and method of administration:

The medicinal product is for single use only.

Zlatal can be injected via the subcutaneous route.

Please also refer to section 6.6.

The overall duration of treatment is decided by the doctor.

The solution is to be visually inspected prior to use.

Only clear solutions practically free from particles should be used.

Any contact of methotrexate with skin and mucosa is to be avoided! In case of contamination, the affected parts are to be rinsed immediately with plenty of water! See section 6.6.

Methotrexate 25 mg/ml treatment of rheumatoid arthritis, juvenile idiopathic arthritis, severe psoriasis vulgaris and psoriatic arthritis represents long-term treatment.

Rheumatoid arthritis

Treatment response in patients with rheumatoid arthritis can be expected after 4-8 weeks. Symptoms may return after treatment discontinuation.

Severe forms of psoriasis vulgaris and psoriatic arthritis

Response to treatment can generally be expected after 2-6 weeks. Depending on the clinical picture and the changes of laboratory parameters, the therapy is then continued or discontinued.

Crohn's Disease:

Response to treatment can be expected after approximately 8 to 12 weeks.

Note:

When switching from oral use to parenteral use, a reduction in the dose may be required, due to the variable bioavailability of methotrexate after oral administration.

Folic acid or folinic acid supplementation may be considered in accordance with current therapeutic guidelines.

4.3 Contraindications

Zlatal is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe hepatic impairment, if serum if bilirubin is > 5 mg/dl (85.5 µmol/l) (see also section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than 30 ml/min., see also sections 4.2 and 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia,
- immunodeficiency,
- serious, acute or chronic infections such as tuberculosis and HIV,
- stomatitis, 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 advised that the therapy is to be administered **once a week**, and not every day. Incorrect intake of methotrexate can lead to severe, including potentially lethal, side effects. Health personnel and patients should be clearly instructed.

Patients receiving therapy should be appropriately monitored, so that signs of possible toxic effects or adverse reactions can be recognised and assessed without delay. Hence, methotrexate should be only administered by, or under the supervision of, doctors whose knowledge and experience include the use of antimetabolite therapy.

Due to the risk of severe or even fatal toxic reactions, the patients should be thoroughly informed by the doctor about the risks (including early signs and symptoms of toxicity) and recommended safety measures. They are to be informed about the necessity to immediately consult the physician if symptoms of intoxication occur as well as about the subsequent necessary monitoring of symptoms of intoxication (including regular laboratory tests).

Doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Skin and mucosal contacts with methotrexate are to be avoided. In the case of contamination, the parts concerned should be rinsed with plenty of water.

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 Zlatal 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.

Recommended examinations and safety measures

Before initiating therapy or upon resuming 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 (in the first two weeks weekly, then every two weeks for the next month; afterwards, depending on leukocyte count and stability of the patient at least once monthly during the next six months and at least every three months thereafter):

Increased monitoring frequency should also be considered when increasing the dose. Particularly elderly patients should be examined for early signs of toxicity in short intervals.

1. Examination of the oral cavity and throat for **mucosal changes**.

2. **Complete blood count** with differential blood count and platelets.

Haematopoietic suppression induced by methotrexate may occur abruptly and at apparently safe doses. In the event of any significant drop in leukocytes or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all signs and symptoms suggestive of infection. In patients concomitantly taking haematotoxic medications (e.g. leflunomide), the blood count and platelets should be closely monitored.

During longer-term therapy with methotrexate bone marrow biopsies are to be performed.

3. **Liver function tests**:

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

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

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

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

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

4. **Renal function** should be monitored via renal function tests and urinanalysis (see sections 4.2 and 4.3).

If serum creatinine is increased, the dose should be reduced. In serum creatinine values above 2 mg/dl, no treatment with methotrexate should be done.

As methotrexate is predominantly excreted via the renal route, increased concentrations can be expected in cases of renal impairment, which may result in severe adverse reactions.

In cases of possible renal impairment (e.g. in elderly patients), closer monitoring is required. This particularly applies to the co-administration of medicinal products which affect methotrexate excretion, cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorders. In the presence of risk factors, such as – even borderline – impaired renal function, concomitant administration of non-steroidal antiphlogistics is not recommended. Dehydration may also potentiate the toxicity of methotrexate.

5. **Assessment of respiratory system**:

Questioning the patient with regard to possible pulmonary dysfunctions, if necessary lung function test.

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non- productive cough), thoracic pain and fever for which patients should be monitored at each follow-up visit. Patients should be informed of

the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

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.

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

Pulmonary diseases induced by methotrexate were not always completely reversible

Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pulmonary diseases induced by methotrexate, like pneumonitis, can occur acutely at any time of therapy, were not always completely reversible and have been reported already at all doses (inclusive low doses of 7.5 mg/week).

During methotrexate therapy, opportunistic infection can occur including pneumocystis carinii pneumonia, which may take a lethal course. If a patient presents with pulmonary symptoms, the possibility of pneumocystis carinii pneumonia should be taken into account.

Special caution is required in patients with impaired pulmonary function.

Particular caution should be exercised in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C), due to possible activation.

6. Methotrexate may, due to its effect on the **immune system**, impair the response to vaccinations and interfere with the result of immunological tests.

Concurrent vaccination using live vaccines must not be carried out.

Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

In patients with pathological accumulation of liquid in body cavities (“third space”), such as ascites or pleural effusions, the plasma elimination half-life of methotrexate is prolonged.

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

Conditions leading to dehydration such as emesis, diarrhoea, stomatitis, can increase the toxicity of methotrexate due to elevated agent levels. In these cases use of methotrexate should be interrupted until the symptoms cease

It is important to identify patients with possibly elevated methotrexate levels within 48 hours after therapy, as otherwise methotrexate toxicity may be irreversible.

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

If haematemesis, black discoloration of the stool or blood in stool occur, therapy is to be interrupted.

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.

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

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).

Photosensitivity

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

Radiation induced dermatitis and sun-burn can reappear during methotrexate therapy (recall reactions). Psoriatic lesions can worsen during UV-irradiation and co-administration of methotrexate.

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

4.5 Interaction with other medicinal products and other forms of interaction

In animal experiments non-steroidal anti-inflammatory drugs (NSAIDs) including salicylic acid caused reduction of tubular methotrexate secretion and consequently increased its toxic effects. However, in clinical studies, where NSAIDs and salicylic acid were given as concomitant medication to patients with rheumatoid arthritis, no increase of adverse reactions was observed. Treatment of rheumatoid arthritis with such drugs can be continued during low-dose methotrexate therapy but only under close medical supervision.

Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the probability of hepatotoxic effects of methotrexate.

Patients taking potentially hepatotoxic and haematoxic medicinal products during methotrexate therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity. Alcohol consumption should be avoided during treatment with Methotrexate 25 mg/ml.

Administration of additional haematotoxic medicinal products increases the likelihood of severe haematoxic adverse reactions to methotrexate. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

Be aware of pharmacokinetic interactions between methotrexate, anticonvulsant drugs (reduced methotrexate blood levels), and 5- fluorouracil (increased t½ of 5-fluorouracil).

Salicylates, phenylbutazone, phenytoin, barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability (indirect dose increase).

Probenecid and mild organic acids may also reduce tubular methotrexate secretion, and thus cause indirect dose elevations, too.

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.

Oral antibiotics such as tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal methotrexate absorption or interfere with the enterohepatic circulation, due to inhibition of the intestinal flora or suppression of bacterial metabolism.

Under (pre-)treatment with substances that may have adverse effects on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Co-administration of medications which cause folate deficiency (e.g. sulphonamides, trimethoprim- sulphamethoxazole) can lead to increased methotrexate toxicity.

Particular caution should therefore also be exercised in the presence of existing folic acid deficiency.

On the other hand, concomitant administration of folinic acid containing drugs or of vitamin preparations, which contain folic acid or derivatives, may impair methotrexate efficacy.

A rise in the toxicity of methotrexate is generally not anticipated when Methotrexate 25 mg/ml is used concomitantly with other antirheumatic agents (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporin).

Though the combination of methotrexate and sulfasalazine may enhance methotrexate efficacy by sulfasalazine related inhibition of folic acid synthesis, and thus may lead to an increased risk of side effects, these were only observed in single patients within several trials.

Co-administration of proton-pump inhibitors such as omeprazole or pantoprazole can lead to interactions:

Concomitant administration of methotrexate and omeprazole has led to a delay in the renal elimination of methotrexate. In combination with pantoprazole, inhibited renal elimination of the 7-hydroxymethotrexate metabolite, with myalgia and shivering, was reported in one case.

Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored under concomitant methotrexate administration.

Excessive consumption of beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, black tea) should be avoided during methotrexate therapy since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

The combined use of methotrexate and leflunomide may increase the risk for pancytopenia. Methotrexate leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dose adjustment.

Particularly in the case of orthopaedic surgery where susceptibility to infection is high, a combination of methotrexate with immune-modulating agents must be used with caution.

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.

Colestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation.

Delayed methotrexate clearance should be considered in combination with other cytostatic agents. Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis.

On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see section 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in females

Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure. As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Pregnancy

Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to have a teratogenic effect in humans; it has been reported to cause foetal death 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 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:

As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see section 4.3). If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

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

CNS symptoms, such as fatigue and confusion, can occur during treatment. Methotrexate 25 mg/ml has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dose level and frequency of Methotrexate 25 mg/ml administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

Most undesirable effects are reversible if recognised early. If such adverse reactions occur, dose should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Frequencies in this table are defined using the following convention:

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).

Further details are given in the following table. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

The following adverse reactions may occur:

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare/ not known**
Infections and infestations					Sepsis, infections (incl. reactivation of inactive chronic infection) may be fatal in some cases
Cardiac disorders				Pericarditis, pericardial effusion, pericardial tamponade	
Blood and lymphatic system disorders		Leukocytopenia thrombocytopenia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders		Severe courses of bone marrow depression, aplastic anaemia. Lymphadenopathy, lymphoproliferative disorders (partly reversible, see "description" below), eosinophilia and neutropenia. First signs for these life-threatening complications may be: fever, sore throat, ulcerations of oral mucosa, flu-like complaints, strong exhaustion, epistaxis and dermatorrhagia. Use of methotrexate should be interrupted immediately if the number of blood cells significantly declines
Immune system disorders			Allergic reactions, anaphylactic shock		Immunosuppression Hypogammaglobulin-aemia
Metabolism and nutrition disorders			Diabetes mellitus		
Psychiatric disorders			Depression, confusion	Mood fluctuations	Insomnia
Nervous system disorders		Headache, fatigue, drowsiness	Vertigo, seizures		Pain, muscular asthenia, paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), acute aseptic meningitis with meningism (paralysis, vomiting) Not known: leukoencephalopathy

Eye disorders				Severe visual disturbances	Conjunctivitis, retinopathy
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas		
Vascular disorders				Hypotension, thromboembolic events	
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever.	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma-like reactions with cough, dyspnoe and pathological findings in the lung function test	Pneumocystis carinii pneumonia and other pulmonary infections, chronic obstructive pulmonary disease. Pleural effusion Not known: pulmonary alveolar haemorrhage.
Gastrointestinal disorders	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24-48 hours after administration of Methotrexate 25 mg/ml). Stomatitis, dyspepsia Stomatitis, dyspepsia	Diarrhoea (especially during the first 24-48 hours after administration of Methotrexate 25 mg/ml).	Gastrointestinal ulcers and bleeding.	Enteritis, melaena Gingivitis, malabsorption	Haematemesis, toxic megacolon

Hepato-biliary disorders	Increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); drop of serum albumin.	Acute hepatitis	Hepatic failure
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	Urticaria, photosensitivity reactions, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque (Psoriatic lesions can exacerbate due to UV radiation during concomitant treatment with methotrexate (also see section 4.4); severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	Increased pigmentary changes of nails, onycholysis, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	acute paronychia, furunculosis, telangiectasia hidradenitis Not known: Skin exfoliation / dermatitis exfoliative
Musculoskeletal system, connective tissue and bone disorders			Arthralgia, myalgia, osteoporosis	Stress fracture	Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia	Proteinuria

General disorders and administration site conditions			After intramuscular use of methotrexate, local adverse reactions (burning sensation) or damage (sterile formation of abscess, destruction of fatty tissue) can occur at the site of injection, disturbed wound healing.		Fever, Subcutaneous administration of methotrexate shows good local tolerance. Only mild local skin reactions, the number of which decreased in the course of treatment, have been observed so far. Not known: injection site necrosis, oedema.
Reproductive system and breast disorders			Inflammation and ulceration of the vagina	Oligospermia, menstruation disorders	Loss of libido, impotence, vaginal discharge, infertility gynaecomastia

Description of selected adverse reactions

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.

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

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions 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 products. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

a) Symptoms of overdose

The adverse toxic effects of methotrexate mainly affect the haematopoietic and gastrointestinal system. Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.

There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

b) Treatment of overdose

Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate. In the event 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 1 hour, and dosing continued until serum levels of methotrexate are below 10-7 mol/L.

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

In patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis arthritis or psoriasis vulgaris, administration of folic or folinic acid may reduce methotrexate toxicity (gastrointestinal symptoms, inflammation of oral mucosa, hair loss and increase of liver enzymes), see section 4.5. Prior to using folic acid products, monitoring of vitamin B12 levels is recommended, since folic acid may mask an existing vitamin B12 deficiency, particularly in adults over 50 years of age.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, other immunosuppressants. ATC-code: L04AX03

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

5.2 Pharmacokinetic properties

Absorption

After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5mg/m2 to 80mg/m2 body surface area), methotrexate

has a mean bioavailability of approximately 70%, although considerable inter- and intra-subject variations are possible (25-100%). Plasma peak concentrations are attained within 1-2 hours. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.

Distribution

Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; under high doses (300mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the liquor. Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites).

Biotransformation

Approximately 10% of the administered methotrexate is metabolised intrahepatically. The major metabolite is 7-hydroxymethotrexate.

Elimination

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced enterohepatic blood flow exists.

In case of renal insufficiency, elimination is delayed significantly. Impaired elimination in presence of hepatic insufficiency is not known.

Methotrexate passes the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity

Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

Mutagenic and carcinogenic potential

Long-term studies in rats, mice and hamsters did not show any evidence of a tumorigenic potential of methotrexate. Methotrexate induces gene and chromosome mutations both in vitro and in vivo. A mutagenic effect is suspected in humans.

Reproductive toxicology

Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to humans occurred.

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

24 months

6.4 Special precautions for storage

Store below 25°C.

Keep the syringe in the outer carton in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

Nature of container:

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with attached injection needle and with a safety device to prevent needlestick injury and re-use. Plunger stoppers of chlorobutyl rubber.

Pack sizes:

Pre-filled syringes containing 7.5 mg (in 0.3 ml), 10 mg (in 0.4 ml), 12.5 mg (in 0.5 ml), 15 mg (in 0.6 ml), 17.5 mg (in 0.7 ml), 20 mg (in 0.8 ml), 22.5 mg (in 0.9 ml) and 25 mg (1.0 ml) methotrexate in solution for injection in packs of 1, 4, 6 and 24.

Packs of 1, 4, 6 and 24 pre-filled syringes contain 2, 8, 12 and 48 alcohol swabs, respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer methotrexate 25 mg/ml.

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

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

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

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2132 WT Hoofddorp

The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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