SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metotab 2.5 mg tablet
Metotab 7.5 mg tablet
Metotab 10 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metotab 2.5 mg: one tablet contains 2.5 mg methotrexate (as methotrexate disodium).
Metotab 7.5 mg: one tablet contains 7.5 mg methotrexate (as methotrexate disodium).
Metotab 10 mg: one tablet contains 10 mg methotrexate (as methotrexate disodium).

Excipient(s) with known effect
Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Yellow, slightly speckled, round, biconvex tablets. The 10 mg tablets have a score line which is for identification only. The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metotab is indicated for the treatment of:

- Severe, active rheumatoid arthritis in adult patients.
- Severe and generalised psoriasis vulgaris, especially of the plaque type, in adult patients who do not respond to conventional therapy.

4.2 Posology and method of administration

Posology

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

The prescriber should specify a weekday for intake on the prescription.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. The overall duration of the treatment is determined by the physician.
The prescriber should ensure that patients or their caregivers will be able to comply with the once weekly regimen.

Concurrent folic acid supplementation of 5 mg twice weekly (except on the day of administration) is indicated additionally.

Posology in adult patients with rheumatoid arthritis
The recommended starting dose is 7.5 mg methotrexate once weekly, administered orally. Depending on the individual activity of the disease and patient tolerance, the initial dose may be increased in increments of 2.5 mg up to a maximum of 25 mg once weekly. Doses exceeding 20 mg/week can be associated with a substantial increase in toxicity, especially bone marrow depression. Response to treatment can be expected after approximately 4–8 weeks. When the desired clinical effect has been achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Patients with psoriasis vulgaris
The recommended starting dose is 7.5 mg methotrexate administered orally once a week. The dose should be increased gradually until the optimum response has been achieved but should not, in general, exceed 25 mg methotrexate per week. Doses exceeding 20 mg/week can be associated with a substantial increase in toxicity, especially bone marrow depression. Response to treatment can generally be expected after approximately 2–6 weeks. When the desired clinical effect has been reached, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Patients with renal impairment
Metotab should be administered with caution to patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	
≥60	100 %
30–59	50 %
<30	Metotab 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. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/l).

Elderly
Dose reduction should be considered in elderly patients due to reduced hepatic and renal function and lower folate reserves with increased age. In addition, close monitoring of patients for possible early signs of toxicity is recommended (see section 4.4).

Method of administration
Metotab is for oral use. The tablet should be swallowed whole with water.

4.3 Contraindications

Metotab is contraindicated in the case of:

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

4.4 Special warnings and precautions for use

The prescriber should specify a weekday for intake on the prescription.
The prescriber should make sure patients understand that Metotab (methotrexate) should only be taken **once a week**.
Patients should be instructed on the importance of adhering to the once-weekly intakes.

Patients undergoing therapy should be monitored in such a way that signs of possible toxic effects or adverse reactions can be detected and evaluated with minimal delay. Therefore methotrexate should only be administered by, or under the supervision of, physicians with knowledge and experience of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, patients should be fully informed of the risks involved and the recommended safety measures.

Lactose
Metotab contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Recommended treatment follow-ups and safety measures

Before starting treatment or reinstituting methotrexate therapy after interruption of treatment
Complete blood count with differential count of platelets, liver enzymes, bilirubin, serum albumin, chest X-ray and renal function tests. If clinically indicated, tuberculosis and hepatitis should be excluded.

During therapy (The tests below must be conducted weekly in the first two weeks, then every two weeks for a month; thereafter, depending on the leucocyte count and the stability of the patient, at least once a month during the first six months and every three months thereafter)
Increased monitoring frequency should be considered also when increasing the dose.

1. Examination of the mouth and throat for mucosal changes.

2. Complete blood count with differential blood count of platelets. Haemopoietic suppression caused by methotrexate can occur suddenly and with apparently safe dose levels. Any marked drop in white blood cell or platelet counts must result in immediate discontinuation of treatment and appropriate supportive therapy. Patients should be advised to report all signs and symptoms of infection. Patients receiving simultaneous treatment with haematotoxic medicinal products (e.g. leflunomide) should undergo close monitoring of blood count and platelets.

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

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

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

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

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

4. Renal function should be monitored by means of renal function tests and urinalysis.
As methotrexate is eliminated primarily via the kidneys, increased serum concentrations can 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 during concomitant treatment with medicines which affect the elimination of methotrexate, or which can cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or affect haematopoiesis. Dehydration can also increase the toxicity of methotrexate.

5. Respiratory tract: Acute or chronic interstitial pneumonitis, often with eosinophilia in the blood, may occur, and deaths have been reported. The symptoms typically include dyspnoea, coughing (especially a dry, non-productive cough) and fever, which will need to be monitored on every follow-up visit. Patients should be informed about the risk of pneumonitis and urged to contact their doctor immediately in the event of persistent cough or dyspnoea. Methotrexate must be discontinued for patients with lung symptoms, and a careful examination (including lung X-ray) performed in order to exclude infection. If methotrexate-induced pulmonary disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be resumed.
Pulmonary involvement requires a quick diagnosis and discontinuation of the treatment.
Pneumonitis can occur at all dosages.
In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and rheumatologic 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 can, due to its effect on the immune system, impair the immune response to vaccination and affect the results of immunological tests. Special attention should also be paid to symptoms indicating possible activation of latent, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C). Concurrent vaccination using live vaccines should not be carried out during treatment with Metotab.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. If the lymphoma fails to show signs of spontaneous regression, cytotoxic therapy is required.

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.

<u>Fertility and reproduction</u>

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 Metotab 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products
The probability of methotrexate-related hepatotoxic effects increases with regular alcohol consumption and concomitant administration of other hepatotoxic medicinal products (see section 4.4). Patients treated concomitantly with other hepatotoxic medicinal products (e.g. leflunomide) should be monitored carefully. The same applies to haematotoxic medicinal products (e.g. leflunomide). The incidence of pancytopenia and hepatotoxicity can increase when leflunomide is combined with methotrexate.
Combined treatment with methotrexate and retinoids such as acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics
Oral antibiotics such as tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation by inhibition of the intestinal flora or suppression of bacterial metabolism.

Antibiotics
Antibiotics such as penicillins, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can in certain cases reduce the renal clearance of methotrexate, which can result in increased serum concentrations of methotrexate with consequent haematological and gastrointestinal toxicity.

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

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents
Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate; as a result higher serum concentrations can be expected, causing increased haematological toxicity. There is also a risk of increased toxicity when a low dose of methotrexate and non-steroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse effects on the bone marrow
During therapy with medicinal products which can cause bone marrow depression (e.g. sulfonamides, trimethoprim-sulfamethoxazole, chloramphenicol, pyrimethamine), attention should be paid to the risk of a marked effect on haematopoiesis.

Medicinal products which cause folate deficiency
Concomitant treatment with products which cause folate deficiency (e.g. sulfonamides, trimethoprim-sulfamethoxazole) can lead to increased side effects from methotrexate. Particular caution is therefore advised in the event of folate deficiency.

Other antirheumatic medicinal products
No increase in the toxic effects of methotrexate is generally to be expected when Metotab is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, ciclosporin).

Sulfasalazine
Although the combination of methotrexate and sulfasalazine can increase the efficacy of methotrexate and at the same time cause more undesirable effects due to the inhibition by sulfasalazine of folic acid synthesis, such undesirable effects have been observed only in rare individual cases in a number of studies.

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

Proton pump inhibitors
Concomitant administration of proton pump inhibitors such as omeprazole or pantoprazole can lead to interactions: concomitant administration of methotrexate and omeprazole has reportedly resulted in delayed renal elimination of methotrexate. In combination with pantoprazole, inhibition of 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.

Beverages containing caffeine or theophylline
Excessive consumption of beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, tea) should be avoided during methotrexate therapy.

4.6 Fertility, pregnancy and lactation

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

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.

In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

- Spontaneous abortions have been reported in 42.5 % of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5 % in disease-matched patients treated with drugs other than methotrexate.

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

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Breast-feeding
Methotrexate is excreted in human milk in concentrations such that there is a risk of an effect on the infant. Thus, methotrexate is contraindicated during breast-feeding (see section 4.3). Breast-feeding should therefore be discontinued prior to and during 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

Effects on the central nervous system such as tiredness and dizziness can occur during treatment. Metotab has an insignificant or moderate effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver

function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Tabulated list of adverse reactions

The undesirable effects are listed below according to frequency:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < /1,000), very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

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

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

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranolocytosis, 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, cognitive dysfunction.
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:	Malabsorption, gingivitis.
Very rare:	Haematemesis, haematorrhoea, toxic megacolon.

Hepatobiliary disorders

Very common:	Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon:	Cirrhosis, liver atrophy, fibrosis and fatty degeneration of the liver, decrease in serumalbumin.
Rare:	Acute hepatitis.
Very rare:	Hepatic failure.

Skin and subcutaneous tissue disorders

Common:	Exanthema, erythema, pruritus.
Uncommon:	Photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare:	Increased pigmentation, petechiae, acne, ecchymosis, allergic vasculitis.
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasias.
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 oogenesis, impaired spermatogenesis, sterility, impaired menstruation, vaginal discharge.

General disorders and administration site conditions

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

Description of selected adverse reactions

The incidence and severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at low doses, it is absolutely essential that patients are monitored by the doctor regularly and 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.

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

[To be completed nationally]

4.9 Overdose

Symptoms of overdose
Toxicity of methotrexate mainly affects the haematopoietic system.
Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions.

Treatment measures in the case of overdose
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the dose of methotrexate administered should be given intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Other immunosuppressants, ATC code: L04AX03

Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis.

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 treatment of psoriasis, psoriatic 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

Methotrexate bioavailability is good (80–100 %) at the low doses used for rheumatoid arthritis and psoriasis. When administered orally, maximum serum concentrations of methotrexate are achieved after 1–2 hours. There is major inter- and intra-individual variation, particularly with repeated dosing.

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

which can persist for weeks or months. At low doses, methotrexate passes into cerebrospinal fluid in minimal quantities.

The mean terminal half-life is 6–7 hours and varies considerably (3–17 hours). The half-life can be prolonged to 4 times the normal length in patients with a third distribution space (pleural effusion, ascites).

Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principal metabolite is 7-hydroxymethotrexate.

Excretion, mainly in unchanged form, is primarily renal via glomerular filtration and active secretion in the proximal tubuli. Approx. 5–20 % methotrexate and 1–5 % 7-hydroxymethotrexate are eliminated via the biliary tract. There is significant enterohepatic circulation.

In patients with renal insufficiency, elimination is delayed significantly. It is not known whether hepatic insufficiency reduces elimination.

There is major inter- and intra-individual variation, particularly with repeated dosing.

5.3 Preclinical safety data

Animal studies have shown that methotrexate impairs fertility and that it is embryotoxic, foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. Since conventional carcinogenicity studies have not been conducted and chronic toxicity studies in rodents have yielded disparate results, methotrexate cannot be classified in terms of its carcinogenicity for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister, containing 10, 30, 50 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2022-03-24