SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate Orion 25 mg/ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 25 mg methotrexate.

1 pre-filled syringe of 0.3 ml solution for injection contains 7.5 mg methotrexate.
1 pre-filled syringe of 0.4 ml solution for injection contains 10 mg methotrexate.
1 pre-filled syringe of 0.6 ml solution for injection contains 15 mg methotrexate.
1 pre-filled syringe of 0.8 ml solution for injection contains 20 mg methotrexate.
1 pre-filled syringe of 1.0 ml solution for injection contains 25 mg methotrexate.

Excipient with known effect: The medicinal product contains maximum 5.21 mg per ml sodium (see section 4.4).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

The medicinal product is a clear, yellowish solution for injection with a pH of 7.0 – 9.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

– Active rheumatoid arthritis in adult patients.

– Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to non-steroidal 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.

– Induction of remission in moderate steroid-dependent Crohn's disease in adult patients, in combination with corticosteroids and for maintenance of remission, as monotherapy, in patients who have responded to methotrexate.

4.2 Posology and method of administration

Important warning about the dosage of Methotrexate Orion (methotrexate)

In the treatment of rheumatic diseases, psoriasis, psoriatic arthritis and Crohn’s disease Methotrexate Orion (methotrexate) **must only be used once a week.** Dosage errors in the use of Methotrexate Orion (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligate.

The patient is to be explicitly informed about the fact of administration **once weekly**. It is advisable to determine a fixed, appropriate weekday as day of injection.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see section 5.2 and 4.4).

Posology

Dosage in patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered either subcutaneously or intramuscularly (see below under "Method and duration of administration"). 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 and psoriatic arthritis
It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions.
The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously or intramuscularly.
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.

Dosage in adult patients with Crohn's disease
- Induction treatment: 25 mg/week administered intramuscularly or subcutaneously.
  Once patients have adequately responded to combination therapy, the corticosteroids should be tapered. Response to treatment can be expected after 8 to 12 weeks.
- Maintenance treatment: 15 mg/week administered intramuscularly or subcutaneously, as monotherapy, if the patient has entered remission.

Special populations

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.

Dosage in 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	Methotrexate must not be used

See section 4.3.

Patients with hepatic impairment
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated (see section 4.3).

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).

Paediatric population

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

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

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

Duration and method of administration

Methotrexate can be given by subcutaneous or intramuscular route. Suitability of intramuscular injection would need to be evaluated individually and depends on the individual thickness of the subcutaneous tissue.
For single use only.

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

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

Special 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 or folinic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications

Methotrexate Orion is contraindicated in:
- Hypersensitivity to methotrexate or to any of the excipients listed in section 6.1
- Severe liver insufficiency (see section 4.2)
- Alcohol abuse
- Severe renal insufficiency (creatinine clearance less than 30 ml/min, see sections 4.2 and 4.4)
- Pre-existing blood dyscrasia, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- 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 informed, that Methotrexate Orion must be administered **once a week**, not every day. Patients should be aware of importance of adhering to the once weekly intakes and that incorrect use of methotrexate can result in severe and even fatal adverse reactions.
Patients undergoing therapy must be appropriately monitored during treatment so that signs of possible toxic effects or adverse reactions can be detected and evaluated with minimal delay. Especially strict monitoring of the patient is indicated following prior radiotherapy (especially of the pelvis), functional impairment of the haematopoietic system (e.g., following prior radio- or chemotherapy), impaired general condition as well as advanced age and in very young children. Therefore, methotrexate should only be 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 treating doctor of the risks involved (including early signs and symptoms of toxicity) and the recommended safety measures. Patients should be informed that they must notify the doctor immediately if any symptoms of an overdose occur and that the symptoms of the overdose need to be monitored (including regular laboratory tests).
Doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Because of the delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate (see sections 4.2 and 4.3).

Methotrexate should be used only with great caution, if at all, in patients who have a significant liver disease, particularly if this is/was alcohol-related (see sections 4.2 and 4.3).

Skin and mucosal contact with methotrexate injection solution is to be avoided.

<u>Fertility and reproduction</u>

<u>Fertility</u>
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.

<u>Teratogenicity – Reproductive risk</u>
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 Methotrexate Orion 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 beginning methotrexate therapy or re-instituting methotrexate therapy after a rest period: Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and hepatic and renal function tests. If clinically indicated, tuberculosis and hepatitis should be excluded.

During therapy (at least once a month during the first six months and every three months thereafter): An increased monitoring frequency should be considered also when the dose is increased.

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

2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white cell or platelet counts indicate immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

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

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13 – 20%. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy. Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, noninvasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient’s comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment.

Additional hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.
Increased caution should be exercised in patients with insulin-dependent diabetes mellitus, as during methotrexate therapy, liver cirrhosis developed in isolated cases without any elevation of transaminases.

4. Renal function should be monitored by renal function tests and urinanalysis (see also sections 4.2 and 4.3):

As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects. In patients with renal impairment the dose of methotrexate should be reduced. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7.

Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least first 24 hours after the administration of methotrexate is started.

Severe renal insufficiency is contraindication for methotrexate therapy (see section 4.3).

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, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation. Dehydration may also intensify 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 symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Methotrexate-induced lung diseases such as pneumonitis can occur acutely and at any time during treatment, are not always completely reversible and have already been observed at all doses (including low doses of 7.5 mg/week).

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination and affect the results of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Concurrent vaccination using live vaccines should not be carried out (see section 4.3).

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.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Following the occurrence of haematemesis, black coloured stools or blood in the stools, treatment must be discontinued.

In addition other conditions leading to dehydration such as emesis, diarrhoea or stomatitis can increase the toxicity of methotrexate due to elevated levels of the active substance. In these cases use of methotrexate should be interrupted until symptoms cease. It is important to determine any increase in

active substance levels within 48 hours of therapy, otherwise irreversible methotrexate toxicity may occur.

If acute methotrexate toxicity occurs, patients may require folinic acid. In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid supplementation may reduce methotrexate toxicity, such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes.

It is recommended to check levels of vitamin B12 prior to initiating folic acid supplementation, particularly in adults aged over 50 years, as folic acid intake may mask a vitamin B12 deficiency.

7. 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 under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) or Stevens-Johnson syndrome have been reported after single or multiple doses of methotrexate.

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.

The 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

Pharmacodynamic interactions

Hepatotoxic agents

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate. If concomitant administration cannot be avoided, patients should be monitored closely for signs and symptoms of liver toxicity including closer monitoring of liver enzymes (see section 4.4). Consumption of alcohol should be avoided or minimised.

Potentially hepatotoxic agents include e.g. retinoids (e.g. acitretin, etrenitate), azathioprin and leflunomide.

Hematotoxic agents

Hematotoxic medicinal products should not be taken during treatment with methotrexate. If concomitant administration cannot be avoided, patients should be monitored closely for signs and symptoms of hematotoxicity including close monitoring of blood count and platelets.

Administration of additional haematotoxic medicinal products increases the likelihood of severe haematotoxic adverse reactions of methotrexate. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided. Concomitant administration with leflunomide increases risk for pancytopenia.

In the case of (pre-)treatment with medicinal products, which may have adverse reactions on the bone marrow (e.g. sulfonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation. Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Medicinal products which affect folate levels and folic acid containing vitamin products

The concomitant administration of products which cause folate deficiency (e.g. sulfonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

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.

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.

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

Ciclosporin

Ciclosporin may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

Pharmacokinetic interactions

Interactions which may increase methotrexate levels

Frequent patient monitoring is necessary especially if high methotrexate doses are administered concomitantly with medicinal products, which reduce methotrexate protein binding, elimination of methotrexate or cause kidney damage. If concomitant use cannot be avoided, consider dose adjustment of methotrexate. Monitoring of methotrexate serum levels may be useful.

Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity.

Methotrexate is plasma protein bound and certain drugs such as oral hypoglycaemics, thiazide diuretics, sulfonamides, phenytoin, barbiturates, tranquilisers, oral contraceptives, amidopyrine

derivatives, doxorubicin, p-aminobenzoic acid, some antibiotics such as penicillin, tetracyclines, chloramphenicol decrease this binding, which can lead to increased toxicity when used concurrently.

There is also a possibility of increased toxicity when low dose methotrexate and non-steroidal anti-inflammatory medicinal products or salicylates are combined. NSAIDs may cause kidney damage.

Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

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.

Penicillins (e.g. amoxicillin), 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 gastrointestinal toxicity may occur.

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment or renal function. Delayed methotrexate clearance should also be considered in combination with other cytostatic medicinal products.

Interactions which may reduce methotrexate levels

Concomitant use of enzyme inducing anticonvulsants (carbamazepine, phenytoin, phenobarbital, primidone) may decrease the methotrexate exposure and impair its therapeutic effect. If used concomitantly, dose adjustment of methotrexate should be considered. Monitoring of methotrexate serum levels may be useful.

Cholestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation. If cholestyramine administration cannot be avoided doses of cholestyramine and methotrexate should be separated as much as possible.

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.

Methotrexate effects on other medicinal products

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

One should be aware of pharmacokinetic interactions between methotrexate and 5-fluorouracil (increased $t_{½}$ of 5-fluorouracil). If coadministration is necessary, patient should be monitored for 5-fluorouracil toxicity and dose adjustments should be considered if necessary.

Radiotherapy

Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis.

Theophylline and caffeine

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

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, 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.

Infection risk and vaccinations

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections (see section 4.3). 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 sections 4.3 and 4.4).

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

4.6 Fertility, pregnancy and lactation

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

Contraception in males

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

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Pregnancy

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

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

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

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

Lactation
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

Central nervous symptoms such as tiredness and dizziness can occur during treatment, therefore in isolated cases methotrexate can have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

In general, the incidence and severity of adverse reactions of methotrexate (MTX) are related to the dose, the dosing frequency, the method of administration and the duration of exposure.

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 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 Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently occurring adverse reactions are leukopenia, anaemia, thrombocytopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. This includes the use of calcium folinate. Methotrexate therapy should only be resumed with particular caution, after careful consideration of the need for treatment and with increased vigilance for the possible recurrence of toxicity.

The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data).

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

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: lymphoma (see “description” below).

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

Immune system disorders
Rare: Allergic reactions, anaphylactic shock.
Not known: Anaphylactic reaction, immunosuppression.

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, paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: encephalopathy/leukoencephalopathy.

Eye disorders
Rare: Visual disturbances, conjunctivitis.
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 which is often associated with eosinophilia (see section 4.4). Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever (see section 4.4).
Uncommon: Pharyngitis.
Rare: Pulmonary fibrosis, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

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

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

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitivity reactions, loss of hair, increase in rheumatic nodules, *herpes zoster*, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare: Increased pigmentation, acne, ecchymosis, petechiae, 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: Hidradenitis, erythema multiforme, onycholysis, skin exfoliation / dermatitis exfoliative.

Lesions of psoriasis may worsen with concomitant UV therapy. Radiation dermatitis and sunburn may be "recalled".

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, infection, wound-healing impairment, hypogammaglobulinaemia.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.
Not known: Chills, asthenia, injection site necrosis, oedema.

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.

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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdosage
Toxicity of methotrexate mainly affects the haematopoietic system.

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, other immunosuppressants
ATC code: L04AX03

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

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 and RNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriatic arthritis, rheumatoid arthritis and Crohn's disease is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

A study of weekly injections of methotrexate in a group of patients with chronically active Crohn's disease (despite at least three months of prednisone therapy), showed that methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone. A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (25 mg weekly) or placebo. After 16 weeks, 37 patients (39.4%) were in clinical remission in the methotrexate group, as compared with 9 patients (19.4%, p = 0.025;) in the placebo group. The patients in the methotrexate group received less prednisone overall and their mean score on the Crohn's Disease Activity Index was significantly lower than those in the placebo group (p = 0.026 and p = 0.002, respectively). [Feagan et al (1995)]

A study of patients, who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate, showed that a low dose of methotrexate maintains remission. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg I.M. once weekly or placebo for 40 weeks. At week 40, 26 patients (65%) were in remission in the methotrexate group and fewer needed prednisone for relapse (28%), as compared with the placebo group (39%; p = 0.04 and 58%, p = 0.01, respectively). [Feagan et al (2000)]

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

5.2 Pharmacokinetic properties

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

Distribution
Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts.

Biotransformation
Approx. 10% of the administered methotrexate dose is metabolised intrahepatically. The principle 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% methotrexate and 1 – 5% 7 hydroxymethotrexate are eliminated biliary. There is pronounced enterohepatic circulation

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).

Special populations
In the case of renal insufficiency, elimination is delayed significantly. Impaired elimination with regard to hepatic insufficiency is not known.

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 tumourigenic 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

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

The medicine is available in pre-filled syringes of colourless glass (type I) of 1 ml capacity with a plunger stopper of chlorobutyl rubber (type I) and attached injection needle and needle shield.

0.3 ml pre-filled syringe, in packs of 1, 4, 5, 6, 10 or 12.
0.4 ml pre-filled syringe, in packs of 1, 4, 5, 6, 10 or 12.
0.6 ml pre-filled syringe, in packs of 1, 4, 5, 6, 10 or 12.
0.8 ml pre-filled syringe, in packs of 1, 4, 5, 6, 10 or 12.
1.0 ml pre-filled syringe, in packs of 1, 4, 5, 6, 10 or 12.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements.
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

Women who are pregnant, planning to be or breast-feeding should not handle methotrexate.

Parents, care givers and patients should be advised to keep methotrexate out of the reach of children, preferably in a locked cupboard.

Accidental ingestion can be lethal for children.

Anyone handling methotrexate should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling methotrexate.

Contact with the skin or mucous membrane must be avoided. If methotrexate comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Spillages must be wiped immediately.

The medicinal product should be visually inspected prior to use. The solution should only be used if it is clear, free from particles and if the container is undamaged.

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

{DD/MM/YYYY}
[to be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-12-13