

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate Astron 50 mg/ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg methotrexate (as methotrexate disodium).

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

Excipient with known effect:

Each pre-filled syringe contains <1 mmol sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, yellow to brown solution.

pH: Between 7.0 to 9.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate 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, who are familiar with the various characteristics of the medicinal product and its mode of action. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the subcutaneous administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligatory. Methotrexate is injected **once weekly**.

The patient must 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).

Dosage in adult patients with rheumatoid arthritis:

The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 – 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis

Children with body surface area below 0.75 m² could not be treated with this product. If lower doses than 7.5 mg are required, another medical product should be used.

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 20mg/m² body surface area/**once weekly**. However, an increased monitoring frequency is indicated if the dose is increased.

Due to limited data availability about intravenous use in children and adolescents, parenteral administration is limited to subcutaneous injection.

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

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

Dosage in patients with psoriasis vulgaris and psoriatic arthritis:

It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Dosage in patients with Crohn's Disease:

- Induction treatment:

25 mg/week administered subcutaneously.

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

- Maintenance treatment:

15 mg/week administered subcutaneously.

There is not sufficient experience in the paediatric population to recommend methotrexate for the treatment of Crohn's Disease in this population.

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
> 50	100 %
20 – 50	50 %
< 20	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.

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 pre-filled syringe is for single use only.
Please note that all of the contents should be used.

Methotrexate solution for injection is given by the subcutaneous route.

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

Instructions for subcutaneous use (see section 6.6)

Note:

If changing from oral to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications

Methotrexate is contraindicated in the case of

- hypersensitivity to methotrexate or to any of the excipients listed in section 6.1,
- severe liver impairment (see section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than 20 ml/min., see section 4.2 and section 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy, breast-feeding (see section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly informed that the therapy should be administered **once a week**, not every day.

Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

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).

Recommended examinations and safety measures

Before beginning or reinstituting methotrexate therapy after a rest period:

Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter):

An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes
2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.
3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.

For psoriasis patients the need for a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged Methotrexate treatment or cumulative doses of 1.5 g or more.

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

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

As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects.

Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, 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: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all dosages.
6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

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

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

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

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

Encephalopathy / Leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

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

The absence of pregnancy should be confirmed before Methotrexate is administered. Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility. These effects appear to be reversible on discontinuing therapy. Effective contraception in men and women should be performed during treatment and for at least six months thereafter. The possible risks of effects on reproduction should be discussed with patients of childbearing potential and their partners should be advised appropriately (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products

The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see section 4.4). Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics

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

Antibiotics

Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding

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

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents

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

Medicinal products with adverse reactions on the bone marrow

In the case of medication with medicinal products, which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency

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

Products containing folic acid or folinic acid

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

Other antirheumatic medicinal products

An increase in the toxic effects of methotrexate is, in general, not to be expected when Methotrexate is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprin, cyclosporin).

Sulphasalazine

Although the combination of methotrexate and sulphasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulphasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Mercaptopurine

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

Proton-pump inhibitors

A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Theophylline

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

Caffeine- or theophylline-containing beverages

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Methotrexate is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported. Women must not get pregnant during methotrexate therapy. In case of women getting pregnant during therapy medical counselling about the risk of adverse reactions for the child associated with methotrexate therapy should be sought. Therefore, patients of a sexually mature age (women and men) must use effective contraception during treatment with Methotrexate and at least 6 months thereafter (see section 4.4).

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. pregnancy test, prior to initiating therapy.

Breast-feeding

Methotrexate is excreted in breast milk in such concentrations that there is a risk for the infant, and accordingly, breast-feeding should be discontinued prior to and throughout administration.

Fertility

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

4.7 Effects on ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, Methotrexate has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Very rare: There have been reports of individual cases of lymphoma which subsided in a number of cases once treatment with methotrexate had been discontinued. In a recent study, it could not be established that methotrexate therapy increases the incidence of lymphomas.

Blood and lymphatic system disorders

Common: Leukopenia, anaemia, thrombopenia.

Uncommon: Pancytopenia.

Very rare: Agranulocytosis, severe courses of bone marrow depression.

Metabolism and nutrition disorders

Uncommon: Precipitation of diabetes mellitus.

Nervous system disorders

Common: Headache, tiredness, drowsiness.

Uncommon: Dizziness, confusion, depression.

Very rare: Impaired vision, pain, muscular asthenia or paraesthesia in the extremities, changes in sense of taste (metallic taste), convulsions, meningism, paralysis.

Unknown: Leukoencephalopathy

Eye disorders

Rare: Visual disturbances.
Very rare: Retinopathy.

Cardiac disorders

Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders

Rare: Hypotension, thromboembolic events.

Respiratory, thoracic and mediastinal disorders

Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.

Rare: Pulmonary fibrosis, *Pneumocystis carinii* pneumonia, shortness of breath and bronchial asthma, pleural effusion.

Gastrointestinal disorders

Very common: Stomatitis, dyspepsia, nausea, loss of appetite.

Common: Oral ulcers, diarrhoea.

Uncommon: Pharyngitis, enteritis, vomiting.

Rare: Gastrointestinal ulcers.

Very rare: Haematemesis, haemorrhage, toxic megacolon.

Hepatobiliary disorders (see section 4.4)

Very common: Elevated transaminases.

Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.

Rare: Acute hepatitis.

Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders

Common: Exanthema, erythema, pruritus.

Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.

Rare: Increased pigmentation, acne, ecchymosis.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, myalgia, osteoporosis.

Renal and urinary disorders

Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.

Rare: Renal failure, oliguria, anuria, electrolyte disturbances.

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: Allergic reactions, anaphylactic shock, allergic vasculitis, fever, conjunctivitis, infection, sepsis, wound-healing impairment, hypogammaglobulinaemia.

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 (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system [to be completed nationally]**.

4.9 Overdose

a) Symptoms of overdosage

Toxicity of methotrexate mainly affects the haematopoietic system.

b) 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: Folic acid analogues

ATC code: L01BA01

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

Mechanism of action

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

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

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

5.2 Pharmacokinetic properties

Absorption

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. Pronounced enterohepatic blood flow exists.

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

Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered **not classifiable** as to its carcinogenicity to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store below 30 °C. Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Nature of container:

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with fixed needle covered with rigid needle shield. Further pre-filled syringes prefixed with needle safety guard. Syringe plungers are made of plunger rod with chlorbutyl rubber stopper.

Pack sizes:

- For 0.15 mL, 0.20 mL, 0.30 mL and 0.40 mL: packs containing 1, 2, 4, 5, 6, 8, 10, 12 and 24 prefilled syringe (s) with fixed needle covered with rigid needle shield. Further pre-filled syringes are prefixed with automatic needle guard.
- For 0.25 mL, 0.35 mL, 0.45 mL, 0.55 mL and 0.60 mL: packs containing 1, 4, 5, 6, 8 and 12 prefilled syringes with fixed needle covered with rigid needle shield. Further pre-filled syringes are prefixed with automatic needle guard.
- For 0.50 mL: packs containing 1, 2, 4, 5, 6, 8, 10 and 12 prefilled syringes with fixed needle covered with rigid needle shield. Further pre-filled syringes are prefixed with automatic needle guard.

All pack sizes are available without graduation marks. Package containing pre-filled syringe (s) with or without blister pack and alcohol swabs. The blister packs are for individual syringes with prefixed automatic needle guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Methotrexate.

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 and please note that all of the contents should be used.

Any unused medicinal product or waste should be disposed of in accordance with local requirements.

Instructions of subcutaneous use.

The best places for the injection are:

- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site (e.g. by using alcohol swab).
2. Pull the protective cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the skin at the same 90 degree angle. The automatic needle guard will cover the needle when releasing the plunger. The automatic needle guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe.

Please note that all of the syringe contents should have to be used; this product is not intended to deliver partial dose.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER

<To be completed nationally>

**9. DATE OF FIRST MARKETING AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

<To be completed nationally>

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