SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARTROJECT 20 mg/2 mL Solution for S.C. Injection in Pre-Filled Syringe
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(for 2 ml)
Active substance:
Contains 21.92 mg methotrexate disodium equivalent to 20 mg methotrexate.
Excipients:
Sodium chloride……..15.4 mg
Sodium hydroxide……q.s. (adequate amount is used for pH 7.5-8.5)
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection
Sterile
Yellow colored, clear and particle-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatological indications:
- Active rheumatoid arthritis in adult patients,
- Polyarthritic forms of active juvenile idiopathic arthritis (JIA) that are inadequately responsive to non-steroidal anti-inflammatory drugs (NSAIDs),
- Active psoriatic arthritis treatment.

Dermatological indications:
- Indicated in the treatment of moderate to severe psoriasis.

Other indications:
- Used in adult Crohn's disease patients with moderately severe steroid dependence, in combination with steroids, for induction of remission or as monotherapy in adult patients responsive to methotrexate, to maintain remission.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
ARTROJECT should only be prescribed by physicians familiar with the various properties and mode of action of this medicinal product. ARTROJECT 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 sections 5.2 and 4.4).

Dosage for adult patients with rheumatoid arthritis and psoriatic arthritis:
The recommended starting dose is 7.5 mg methotrexate administered subcutaneously or orally once a week. Depending on the individual's disease activity and the patient's tolerance, the starting dose may be gradually increased by 2.5 mg per week, but the weekly dose should not exceed 30 mg. However, doses exceeding 20 mg/week are associated with a significant increase in toxicity, particularly bone marrow suppression. A response to treatment can be expected after approximately 4-8 weeks. Once the desired therapeutic outcome is achieved, the dose should be gradually reduced to the lowest effective maintenance dose.

Dosage for patients with psoriasis:
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 may be increased gradually but should not, in general, exceed a weekly dose of 25 mg. However, doses exceeding 20 mg/week are associated with a significant increase in toxicity, particularly bone marrow suppression. A response to treatment can be expected after approximately 2-6 weeks. Once the desired therapeutic outcome is achieved, the dose should be gradually reduced to the lowest effective maintenance dose.

Dosage in patients with Crohn's Disease:
- Induction treatment:

25 mg/week administered subcutaneously
- Maintenance treatment:

15 mg/week administered subcutaneously

A response to treatment can be expected after approximately 8-12 weeks.

There is insufficient experience with the use of ARTROJECT for the treatment of Crohn's disease in the pediatric population.

Method of administration:
This medicinal product is for single use only.

ARTROJECT is administered subcutaneously.

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

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.

Additional information on special populations
Renal impairment:
ARTROJECT should be used with caution in patients with impaired renal function. Dose adjustment should be made according to the table below:

Creatinine clearance (mL/min)	Dose
>50	%100
20-50	%50
<20	ARTROJECT must not be used.

Hepatic impairment:
ARTROJECT should be administered with caution in patients with current or previous liver disease, especially if due to alcohol. If bilirubin is >5 mg/dL (85.5 micromole/L), ARTROJECT is contraindicated.

Pediatric population:
Dosage in children below 16 years with polyarthritic forms of juvenile idiopathic arthritis:
The recommended dose is 10-15 mg/m^2 body surface area (BSA) given orally or subcutaneously once a week. If there is no response to treatment, the weekly dose may be increased to 20 mg/m^2 (BSA). However, since doses exceeding 20 mg/week are associated with a significant increase in toxicity, especially bone marrow suppression, monitoring frequency should be increased and the total dose should not exceed 25 mg per week. Once the desired therapeutic result is achieved, the dose should be gradually reduced to the lowest effective maintenance dose.

Children/adolescents with juvenile idiopathic arthritis should always be referred to a rheumatologist for treatment.

Efficacy and safety have not been evaluated in children under 3 years of age.

Geriatric population:
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patients with a third distribution space (pleural effusions, ascites):
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 sections 5.2 and 4.4).

4.3 Contraindications
ARTROJECT is contraindicated in the following conditions:
- 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 sections 4.2 and 4.4)
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
- Serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes
- Ulcers of the oral cavity and known 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 the therapy has to be administered once a week, not every day. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of

severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Due to insufficient experience with efficacy and safety in children under 3 years of age, the drug is not recommended for use in this age group (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 monthly for 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. Hemopoietic 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 hematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. Liver function tests: Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks after which treatment may be resumed at the discretion of the doctor. The use of liver biopsy for monitoring hepatic toxicity in rheumatic indications is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The need for liver biopsy before or during treatment for psoriasis patients should be evaluated according to current scientific data. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. 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 or cumulative doses of 1.5 g or more.

   Screening for liver-related enzymes in serum: 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 %. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

   Due to the potentially toxic effect on the liver, additional hepatotoxic medications should not be given during treatment with methotrexate unless clearly necessary and alcohol consumption should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medications (e.g. leflunomide). The same should also be taken into consideration if hematotoxic medications are co-administered.

4. Renal function should be monitored by renal function tests and urinanalysis (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, dyspnea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. Pulmonary disease requires rapid diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all doses.

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).

Diarrhea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise hemorrhagic 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.

Before applying ARTROJECT, it is necessary to make sure that the patient is not pregnant. Methotrexate causes embryotoxicity, abortion and fetal defects in humans. Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may lead to decreased fertility. These effects are reversible if treatment is not continued. Effective contraception should be used in both men and women throughout treatment and for at least 6 months after treatment. Therefore, the possible risks of effects on reproduction should be discussed with female patients of childbearing potential, and spouses should be appropriately warned (see section 4.6).

This medicinal product contains less than 23 mg (1 mmol) sodium per dose; that is to say essentially "sodium free".

4.5 Interactions with other medicinal products and other forms of interaction

Levetiracetam

Concomitant administration of levetiracetam and methotrexate has been reported to reduce methotrexate clearance, thereby increasing/prolonging methotrexate concentrations in the blood to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients receiving these two drugs together.

Alcohol, hepatotoxic medicinal products, hematotoxic 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 (e.g. leflunomide) concomitantly should be monitored with special care. The same should be taken into account with the simultaneous administration of hematotoxic 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 hematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding

Methotrexate is plasma protein bound and may be displaced by other protein bound medicinal products such as salicylates, hypoglycemics, 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 hematological 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 ARTROJECT is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprin, and cyclosporine).

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 may decrease the clearance of theophylline. 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.

Additional information on special populations
There are no interaction studies with special populations.

Pediatric population
No interaction studies are available in the pediatric population.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category: X

Women of child-bearing potential/ Birth control (Contraception)
Women must not get pregnant during methotrexate therapy. If pregnancy occurs during treatment, medical information should be sought about the risks of adverse reactions in children associated with methotrexate therapy. Therefore, sexually mature patients (male or female) must use an effective contraception during treatment with ARTROJECT and at least 6 months thereafter (see section 4.4).

For women of childbearing age, it should be absolutely assured that these women are not pregnant by taking appropriate precautions, such as performing a pregnancy test before treatment.

Pregnancy
ARTROJECT 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 fetal death and/or congenital abnormalities. In a limited number of pregnant women (42), exposure resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular, and extremity).When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Lactation
Methotrexate is excreted in human milk at a concentration that may pose a risk to the infants, therefore breast-feeding must be discontinued prior to and throughout administration.

Fertility
Because methotrexate is genotoxic, women wishing to become pregnant are advised to seek genetic counseling and men should seek advice on the possibility of preserving their sperm prior to treatment.

4.7 Effects on ability to drive and use machines
Central nervous symptoms such as tiredness and dizziness can occur during treatment. ARTROJECT 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 hematopoietic system and gastrointestinal disorders.

The following headings are used to organize the undesirable effects in order of frequency: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10.000 to <1/1.000); very rare (<1/10.000), not known (cannot be estimated from the available data).

Neoplasms, benign and malignant (including cysts and polyps)
Very rare: Decreased incidence of lymphoma has been reported when methotrexate therapy was 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, anemia, thrombopenia
Uncommon: Pancytopenia
Very rare: Agranulocytosis, severe courses of bone marrow depression

Metabolism and nutrition disorders
Uncommon: Triggering of diabetes mellitus

Nervous system disorders
Common: Headache, tiredness, drowsiness
Uncommon: Dizziness, confusion, depression
Very rare: Visual impairment, pain, muscular asthenia or paresthesia of the extremities, changes in sense of taste (metallic taste), convulsions, meningitis, paralysis
Not known: 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, diarrhea
Uncommon: Pharyngitis, intestinal inflammation, vomiting
Rare: Gastrointestinal ulcers
Very rare: Hematemesis (vomiting blood), hematorrhea, toxic megacolon

Hepatobiliary disorders
Very common: Elevation of 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: Photo sensitization, 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 bladder, renal impairment, urinary incontinence
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, gynecomastia, oligospermia, impaired menstruation, vaginal discharge

General disorders and administration site conditions
Rare: Allergic reactions, anaphylactic shock, allergic vasculitis, fever, conjunctivitis, infection, sepsis, slowed wound healing, hypogammaglobulinemia
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following subcutaneous administration

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.

Only mild local skin reactions were observed, decreasing during therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

4.9 Overdose
a) Symptoms of overdosage
Toxicity of methotrexate mainly affects the hematopoietic system.

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

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

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

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.

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

5.2 Pharmacokinetic properties

General properties
Absorption:
Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable inter-individual and intra-individual deviations are possible (25-100 %). Maximum serum concentrations are achieved after 1-2 hours.

Bioavailability of subcutaneous 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 body fluid in minimal amounts. The terminal half-life is on average 6-7 hours and demonstrates considerable variation (3-17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Biotransformation:
Approx. 10 % of the administered methotrexate dose is metabolized intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination:
Excretion takes 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.

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

Linearity/non-linearity:
No information available.

5.3 Preclinical safety data
Animal studies show that methotrexate impairs fertility, also is embryotoxic, fetotoxic 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 animals 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 injection

6.2 Incompatibilities
Compatibility studies with other parenteral products have not been conducted. This medicinal product should not be mixed with other medicinal products and solvents.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Should be stored at room temperature below 25°C.
Pre-filled syringes should be stored in their packaging to protect from light.

6.5 Nature and contents of container
Supplied with 1 injection needle, 1 pre-filled syringe with a capacity of 2.25 mL, and a patient leaflet, all in a cardboard box.

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 ARTROJECT.

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.

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

It should not be used when precipitate is observed.

For single use only. Unused solution must be discarded.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2018/235

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 27.04.2018
Date of last renewal:

10. DATE OF REVISION OF THE TEXT