SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2mg/ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 2.19mg Methotrexate disodium equivalent to 2mg Methotrexate.

Excipients with known effect
Sodium Methyl Parahydroxybenzoate (E219) – 1.1mg/ml
Sodium Ethyl Parahydroxybenzoate (E215) – 0.54mg/ml
Propylene Glycol (from the flavour) (E1520) – 1.93mg/ml
Sulphites (from the flavour)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A clear yellow oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate 2mg/ml Oral Solution is indicated in the following oncological indications:

- The maintenance treatment of Acute Lymphocytic Leukaemia (ALL) in children and adults.
- The treatment of malignant trophoblastic tumours

Methotrexate 2mg/ml Oral Solution is indicated in:

- The treatment of severe active rheumatoid arthritis in adults.
- Polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA) in adolescents and children aged 3 years and over when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.

- The treatment of severe forms of psoriasis vulgaris including chronic plaque psoriasis, erythrodermic psoriasis, psoriatic arthritis and pustular psoriasis which are not responsive to other conventional therapies such as phototherapy, PUVA and retinoids.

4.2 Posology and method of administration

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

Important warning about the dosage of methotrexate

In the treatment of rheumatoid arthritis, including JIA and psoriasis, methotrexate **must only be used once a week.** Dosage errors in the use of methotrexate can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

In the treatment of rheumatoid arthritis, including JIA and psoriasis, the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. The prescriber should specify the day of intake on the prescription.

Treatment with ‘Methotrexate 2 mg/ml oral solution should be initiated and supervised by physicians with experience in antimetabolite chemotherapy and the management of the approved indications. The treatment regimen should be decided on an individual patient basis, with reference to current treatment protocols.

During treatment with methotrexate patients require careful monitoring to avoid severe toxicities and to ensure fast identification of toxic side effects. Measurement of serum methotrexate level is absolutely essential.

Pharmaceutical forms with lowest possible strength should be used. Fatal cases of intoxication have been reported after intravenous and intrathecal administration of incorrect calculated doses. Therefore, dosage must be carefully calculated in all patients.

The application and dosage recommendation for the administration of methotrexate for different indications varies considerably. Some common dosages and therapy protocols, which have proved to be efficacious in the therapy of the disorder in each case, are given below. Current published protocols should be always consulted for the dosages and the method and sequence of administration.

Doses in excess of 100 mg are usually given by intravenous infusion.

Skin and mucus membrane contact with methotrexate should be avoided. If methotrexate contaminates the skin it should be washed off immediately using copious amounts of running water for at least ten minutes.

Posology

Dosage for Rheumatoid arthritis

IMPORTANT: For rheumatic conditions, this medicine should be taken once a week. Incorrect dosing may lead to serious adverse effects including fatalities.
The prescriber may specify the day of intake on the prescription.

Dosage in adult patients with rheumatoid arthritis
The usual dose is 7.5 – 15 mg (3.75 ml – 7.5 ml) once weekly. The schedule may be adjusted gradually by 2.5mg weekly, depending on the individual activity of the disease and tolerability by the patient to achieve an optimal response but should not exceed a total weekly dose of 20 mg (10 ml). Thereafter the dose should be reduced to the lowest possible effective dose which in most cases is achieved within 6 weeks.

Response to treatment can be expected after approximately 4-8 weeks.

Symptoms may return after treatment discontinuation.

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

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

The recommended dose is 10 – 15 mg (5 – 7.5 ml)/m^2 body surface area (BSA)/week. In therapy-refractory cases the weekly dosage may be increased to 20 mg (10 ml)/m^2 BSA/week. However, increased monitoring frequency is indicated if the dosage is increased.

The treating physician will decide how long the patient should be treated. Treatment of severe active rheumatoid arthritis and severe JIA represents a long-term treatment.

Dosage in oncological indications (low dose therapy: single dose < 100 mg/m^2)
Doses are usually based on the patient's body surface area (BSA).

Doses in excess of 100 mg are usually given parenterally, when an injectable preparation should be used.

A test dose of 5 - 10 mg parenterally is recommended, one week prior to therapy to detect idiosyncratic adverse events.

Malignant Trophoblastic Tumours:
15mg/m^2, Day 1 to Day 5. Usually such courses may be repeated 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside.

Acute Lymphocytic Leukaemia
Low-dose methotrexate is used in the maintenance treatment of acute lymphocytic leukaemia in children and adults within complex protocols in combination with other cytostatic medicinal products for maintenance treatment.
Common accepted single doses lie in the range of 20- 40mg/m^2 body surface area.

If methotrexate is administered in combination chemotherapy regimens, the dosage should be reduced, taking into consideration any overlapping toxicity of the other drug components.

Dosage for psoriasis:
Before starting treatment it is advisable to give the patient a test dose of 2.5 – 5.0 mg to exclude unexpected toxic effects. If, one week later, appropriate laboratory tests are normal, treatment may be initiated. The recommended initial dose is 7.5 mg (3.75 ml) methotrexate once weekly. The usual dose is 10mg – 25mg (5ml – 12.5ml) taken once weekly. As necessary, the total weekly dose can be increased up to a maximum dose of 25mg once weekly. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which is most cases is achieved within 4 to 8 weeks. Doses exceeding 20 mg (10 ml) per week can be associated with significant increase in toxicity, especially bone marrow suppression.

The treating physician will decide how long the patient should be treated. Treatment of psoriasis and psoriatic arthritis represents a long-term treatment.

The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy (see section 4.4). The aim of therapy should be to reduce the dose to the lowest possible level with the longest rest period. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged.

Special Populations

Elderly
Methotrexate should be used with extreme caution in elderly patients, a reduction in dosage should be considered due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age. In addition, close monitoring of elderly patients for possible early signs of toxicity is recommended (see sections 4.4, 4.5, 4.8 and 5.2).

Hepatic impairment
Methotrexate should be administered only with the greatest caution, if at all, in patients with significant existing or previous liver disease, especially if due to alcohol. If bilirubin levels are >5 mg/dl (85.5 µmol/l), methotrexate is contraindicated (see sections 4.3 and 4.4).

Patients with renal impairment
Since methotrexate is predominantly eliminated renally, in patients with impaired creatinine clearance, delayed elimination is to be expected, which can lead to severe

side effects. In patients with impaired renal function, the dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations. Renal function can be adversely affected by the application of methotrexate. Methotrexate should be used with caution in patients with impaired renal function.

The following dose adjustments apply to patients with renal impairment with the indication of psoriasis / psoriatic arthritis and the indication of rheumatoid arthritis and juvenile idiopathic arthritis. For the oncology indications, recommendations in published protocols should also apply.

Creatinine-Clearance (ml/min)	**% of standard dose**
≥ 60	100
30-59	50
< 30	Methotrexate 2mg/ml Oral Solution must not be used.

Patients with pathological fluid accumulations (pleural effusion, ascites)
As the half-life of methotrexate can be prolonged four-fold in patients with pathological fluid accumulations, it may be necessary to reduce the dose and in some cases even to discontinue methotrexate (see sections 4.4 and 5.2). The amount of dose reduction should be decided on a case-by-case basis.

Paediatric population

Oncological indication
Methotrexate should be used with caution in children. Standard therapy protocols should be consulted for dosages and method and sequence of administration. Fatal cases of intoxication have been reported after intravenous and intrathecal administration of incorrect calculated doses. Therefore, dosage must be carefully calculated in children.

Non-oncological indications
Polyarthritic forms of juvenile idiopathic arthritis:
Use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this patient group.

Psoriasis:
Safety and efficacy in children and adolescents have not been established. Therefore, the use of Methotrexate 2mg/ml Oral Solution is not recommended.

Method of administration
The medicine is for oral administration only.
The medicine should be administered using the syringe provided in the pack or as directed by the healthcare professional. (See Section 6.6)
Methotrexate can be taken with or without food.
Once the dose has been swallowed, a glass of water should be drunk to remove any methotrexate residue from the oral cavity.
If the oral route is ineffective, a change to a parenteral dosage form is indicated. This can be done with methotrexate as an intramuscular or subcutaneous administration

and is recommended for patients who exhibit inadequate absorption of the oral form of methotrexate or who do not tolerate oral administration well.

4.3 Contraindications

Methotrexate is contra-indicated in the following:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- severe renal impairment (creatinine clearance less than 30 ml/min, see section 4.2)
- significant hepatic impairment (bilirubin levels are >5 mg/dl [85.5 µmol/l], see section 4.2)
- alcoholism
- active infectious disease
- overt or laboratory evidence of immunodeficiency syndrome(s)
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or serious anaemia
- severe, acute or chronic infections such as tuberculosis and HIV
- stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcers
- breast-feeding (see section 4.6)
- during methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

Additionally for non-oncological indications:

- Pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

The oral solution contains 2 mg of methotrexate in each ml of solution; the scaling of the dosing syringe is in ml and not mg; care should be taken that the correct dosing volume is prescribed. Patients with rheumatological or dermatological diseases must be informed unequivocally that treatment is to be taken just once a week and not daily. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Medical staff and patients must be clearly instructed.

Warnings regarding non-oncological indications

The prescriber should specify the day of intake on the prescription.

The prescriber should make sure patients understand that methotrexate should only be taken once a week.

Patients should be instructed on the importance of adhering to the once-weekly intake.

Patients must be appropriately monitored during treatment so that signs of possible toxic effects or adverse reactions can be detected and evaluated with minimal delay.

Therefore, methotrexate should only be administered by, or under the supervision of, doctors whose knowledge and experience includes treatment with antimetabolites. 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.

Because of the possibility of severe or even fatal toxic reactions, patients should be extensively 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 (10 ml)/week can be associated with a substantial increase in toxicity, especially bone marrow depression.

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 section 4.2).

Methotrexate should be used only with great caution, if at all, in patients who have significant liver disease, particularly if this is/was alcohol-related.

Fertility
Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age (see section 4.6).

In non-oncologic indications, the absence of pregnancy must be confirmed before methotrexate is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Precautions

Recommended examinations and safety measures

Before initiating therapy or resuming treatment after a recovery period
Before administration of methotrexate, the following check-up examinations and safety precautions are recommended:

- renal and hepatic function tests including serum albumin
- a complete blood count including differential count and platelets
- urinalysis should be performed as part of the prior and follow-up examinations
- chest x-ray
- hepatitis A, B, C serology
- tuberculosis diagnostics

Strict monitoring is necessary in patients with pulmonary dysfunction. 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.

During Therapy

The tests below must be conducted weekly in the first two weeks, then every two weeks for a month; thereafter, depending on the leucocyte count and the stability of the patient, at least once a month during the next six months and then at least every three months.

An increased monitoring frequency should be considered when the dose is increased. In particular, elderly patients should be monitored at short intervals for early signs of toxicity (see section 4.2).

Examination of the mouth and throat for mucosal changes.

Complete blood count with differential blood count and platelets
Methotrexate-induced haematopoietic suppression may occur abruptly and with apparently safe dosages. Any serious decrease in leucocyte or platelet counts indicates the immediate discontinuation of treatment and appropriate supportive therapy. Initial clinical signs for life-threatening complications of severe cytopenia include fever, sore throat, oral ulcerations, flu-like symptoms, nasal and dermal bleedings. Patients should be encouraged to report all signs and symptoms suggestive of infection to their doctor. In patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide), blood count and platelets should be closely monitored.

The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential. Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.

Methotrexate should be used with extreme caution in patients with infection, haematological depression, renal impairment, diarrhoea, ulcerative disorders of the GI tract and psychiatric disorders. If profound leukopenia occurs during therapy, bacterial infection may occur and become a threat.

Liver function tests

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

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

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

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

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

Respiratory

Strict monitoring is necessary in patients with pulmonary dysfunction, smokers and/or patients with certain bronchopulmonary diseases, particularly bronchiectasis or fibrosis. It is recommended to perform lung function tests prior to initiating treatment. In all cases, a chest x-ray should be performed before starting treatment with methotrexate.

Methotrexate should be withdrawn from patients with pulmonary symptoms, and a thorough investigation 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.

Reversible eosinophilic pulmonary reactions and treatment-resistant, interstitial fibrosis may occur, particularly after long-term treatment.

Methotrexate elimination is reduced in patients with pathologic fluid accumulation (third space fluids) such as ascites or pleural effusions that may lead to prolonged methotrexate plasma elimination half-life and unexpected toxicity. Patients with

pleural effusions and ascites should be drained prior to initiation of methotrexate therapy. Methotrexate dose should be reduced according to the serum methotrexate concentrations

Acute or chronic pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, hypoxaemia,cough (especially a dry productive cough) 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.

Lung manifestations of RA and other connective tissue disorders are recognised to occur. In patients with RA, the physician should be specifically alerted to the potential for methotrexate induced adverse effects on the pulmonary system.
Pulmonary symptoms require a rapid 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 (3.75 ml)/week).

Opportunistic infections can occur during treatment with methotrexate, including Pneumocystis jiroveci pneumonia, which can also have a fatal outcome. If a patient develops pulmonary symptoms, the possibility of Pneumocystis jiroveci pneumonia should be considered.

Particular caution is required in patients with impaired pulmonary function.

Particular caution is also required in the presence of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur.

Alcohol intake
Due to its hepatotoxic potential it is recommended that patients abstain from or at least significantly reduce alcohol use. In addition, patients should not receive concomitantly other hepatotoxic or potentially hepatotoxic drugs.

Diabetes mellitus
Patients with insulin-dependent diabetes should only cautiously be treated with methotrexate since cases of liver cirrhosis without intermittent increases in liver enzymes have been reported.

Gastrointestinal
Particular care and possible cessation of treatment are indicated if stomatitis or GI toxicity occurs as haemorrhagic enteritis due to the danger of potentially fatal intestinal perforation.

Conditions leading to dehydration like vomiting, diarrhoea or stomatitis can increase toxic effects due to elevated methotrexate levels. In these cases a supportive treatment should be implemented and discontinuation of methotrexate treatment should be considered.

It is important to determine any increase in active substance levels within 48 hours of therapy, otherwise irreversible methotrexate toxicity may occur.

Diarrhoea and ulcerative stomatitis may be signs of toxic effects and require the discontinuation of treatment, 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.

Renal function, renal impairment and patients at risk of renal impairment

Renal function should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced. If creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given (see sections 4.2 and 4.3).

Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started.
As methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions.

If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly.

If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate.

Live vaccines
Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause severe antigenic reaction and is therefore contraindicated (see 4.3).

Encephalopathy/leukoencephalopathy
Since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer 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.

Malignancy
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. There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. In a recent study, no increased incidence in the manifestation of lymphomas during the course of methotrexate treatment could be detected. Furthermore, the potential of methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a carcinogenic risk.

For contraception advice for men see section 4.6.

Skin toxicity
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.

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 sunburn can reappear during methotrexate therapy (recall reactions). Psoriatic lesions can worsen during UV radiation and co-administration of methotrexate.

Folic acid supplementation:
If acute methotrexate toxicity occurs, patients may require treatment with 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.

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Vitamin products

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

Excipient Warnings
This product contains:

- Sodium Methyl and Ethyl Parahydroxybenzoate (E219 and E215) – May cause allergic reactions (possibly delayed)
- Propylene Glycol (E1520) – This medicine contains 1.93mg propylene glycol in each 1ml dose.
- Sulphites (from the flavour) – May rarely cause severe hypersensitivity reactions and bronchospasm
- This medicine contains less than 1 mmol sodium (23mg) per 1ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

After absorption methotrexate binds partly to serum albumin. Salicylates, amidopyrine derivatives, phenylbutazone, diphenylhydantoin (phenytoin), barbiturates, tranquillisers, tetracyclines, sulphonamides, doxorubicin, probenecid, p-aminobenzoic acid, oral contraceptives, antidiabetic agents and thiazide diuretics displace methotrexate bound to the plasma protein and can increase its toxicity. Therefore, great caution should be exercised when these medicinal products are coadministered with methotrexate.

Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

In the case of pre-treatment with medicinal products exhibiting myelosuppressive or immunosuppressive effects (e.g. cytostatics, metamizole, pyrimethamine sulphonamides, chloramphenicol, diphenylhydantoin, amidopyridine derivatives), it is possible to observe enhancement of bone marrow toxicity and immunosuppression. Bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were coadministered. Sulfonamides and trimethoprim/sulfamethoxazole have been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect. Conversely, co-administration of medicinal products containing folinic acid or vitamin preparations containing folic acid or derivatives may impair the efficacy of methotrexate.

The possibility of delayed methotrexate clearance should be considered in combination with other cytostatic medicinal products.

The application of pyrimethamine and cotrimoxazole (trimethoprim) in combination with methotrexate can cause acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofolic acid reductase.

Sequential use of methotrexate and 5-fuorouracil may result in synergistic enhancement of cytotoxic effects.

Pharmacokinetic interactions between methotrexate, anticonvulsants (reduced serum methotrexate levels) and 5-fluorouracil (increased half-life of 5-fluorouracil) must be borne in mind.

Probenecid and weak organic acids can also reduce the tubular secretion of methotrexate and thus likewise cause an indirect increase in dose.

Penicillins (e.g. amoxicillin, carbenicillin, mezlocillin) and other antibiotics (e.g. glycopeptides, sulphonamides, ciprofloxacin and cefalotin) can decrease the renal clearance of methotrexate in some cases and haematological and gastrointestinal toxicity has been observed in combination with high- and low-dose methotrexate.

Oral antibiotics, such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of methotrexate by bacteria.

Coadministration of other, potentially nephro- and hepatotoxic agents (e.g. sulfasalazine, leflunomide and alcohol) with methotrexate should be avoided. Special caution should be exercised when observing patients receiving methotrexate therapy in combination with azathioprine or retinoids. The consumption of alcohol should be avoided during treatment with methotrexate (see section 4.4). Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the likelihood of hepatotoxic adverse reactions to methotrexate.

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

Methotrexate in combination with leflunomide can increase the risk for pancytopenia.

Enhancement of nephrotoxicity may be seen with high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

NSAIDs should not be administered before or concurrently with high-dose methotrexate. Concomitant use of some NSAIDs and high-dose methotrexate has been reported to increase and prolong the serum methotrexate concentration in serum and to increase gastrointestinal and haematological toxicity. If combined treatment is required, the blood count and renal function should be monitored. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours, since in this case methotrexate plasma levels can rise and toxicity be increased as a result. When using smaller doses of methotrexate, these medicinal products have been found in animals to decrease the tubular secretion of methotrexate and possibly to increase its

toxicity. In addition to methotrexate, patients with rheumatoid arthritis have generally been treated, however, with NSAIDs with no problems. It should be noted, however, that the doses of methotrexate used in the treatment of rheumatoid arthritis (7.5 – 15 mg/week) are slightly lower than those used for psoriasis and that higher doses can result in unexpected toxicity.

In the presence of an existing folic acid deficiency, the toxicity of methotrexate is increased, the efficacy of therapy can be impaired by tetrahydrofolic acid preparations. Concomitant therapy with medicinal products that can cause folic acid deficiency (e.g. sulphonamides, trimethoprim/sulphamethoxazole) can result in increased methotrexate toxicity. Vitamin preparations containing folic acid or its derivatives may change the response to methotrexate.

The combination of methotrexate and sulfasalazine can enhance the effect of methotrexate, as sulfasalazine causes inhibition of folic acid synthesis. This can result in an increased risk of adverse reactions, although in several studies this was only observed in individual patients.

There is evidence that coadministration of methotrexate and omeprazole prolongs the elimination of methotrexate via the kidneys. Coadministration of proton pump inhibitors, such as omeprazole or pantoprazole, can cause interactions. In one case in which methotrexate was combined with pantoprazole, renal elimination of the metabolite 7-hydroxymethotrexate was inhibited and myalgia and shivering occurred. Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeinated beverages, black tea) should be avoided during methotrexate therapy as the effect of methotrexate may be reduced by the possible interaction between methotrexate and methylxanthines at the adenosine receptors.

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

Methotrexate may increase the bioavailability and plasma levels of mercaptopurine. By interference with first-pass metabolism. Combinations of methotrexate and mercaptopurine may therefore require dose adjustment.

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections. In view of its possible effects on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to assess the immune reaction). Concomitant use with a live vaccine is contra-indicated (see Section 4.3)

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

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

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment or renal function.

Patients receiving concomitant therapy with methotrexate and acitretin or other retinoids should be monitored closely for any possible increased risk of hepatotoxicity.

In patients receiving methotrexate therapy, treated for a cutaneous herpes zoster with adrenocortical steroids, in isolated cases, disseminated herpes zoster manifested.

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

Concomitant application of L-asparaginase is antagonistic towards the effects of methotrexate.

Care should be taken when erythrocyte concentrates are administered concomitantly with methotrexate. In patients infused with methotrexate over 24 hours and who subsequently received blood transfusions, increased toxicity was observed, caused by prolonged high serum concentrations of methotrexate.

Particularly in the case of orthopaedic surgery where the risk of infection is high, combination therapy with methotrexate and immunomodulatory medicinal products must be used with caution.

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

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 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, in particular at doses commonly used in oncologic indications

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

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.

As methotrexate is 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.

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 starting 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. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Central nervous symptoms such as tiredness, drowsiness 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 side effects are considered to be dose-related.

In the antineoplastic treatment myelosuppression and mucositis are the predominant dose-limiting toxic effects of methotrexate. The severity of these reactions depends on the dose, mode and duration of application of methotrexate. Mucositis generally appears about 3 to 7 days after methotrexate application, leucopenia and thrombocytopenia follow a few days later. In patients with unimpaired elimination mechanisms, myelosuppression and mucositis are generally reversible within 14 to 28 days.

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

The most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite) and abnormal liver function tests (e.g. increased alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Most adverse reactions are reversible if they are detected early. If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate (see sections 4.2 and 4.4). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Methotrexate has the potential for serious, sometimes fatal toxicity. The toxic effects may be related in frequency and severity to the dose and frequency of administration but have been seen at all doses. Because the toxic reactions can occur at any time during therapy and even at lover doses, patients have to be observed closely and must be informed of early signs and symptoms of toxicity.

Methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy. It is not always fully reversible. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation.

The frequencies of the adverse reactions are classified as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions for the various systems are as follows:

	Very common	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations		Infections	Opportunistic infections (sometimes fatal)	Herpes Zoster	Sepsis, Cytomegalovirus-induced infections	Disseminated herpes simplex, Nocardiosis, Histoplasmosis, Cryptococcosis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Lymphoma[1]			
Blood and lymphatic system disorders		Leucopenia, Thrombocytopenia, Anaemia	Pancytopenia, Agranulocytosis, haematopoietic disorders	Megaloblastic anaemia	Lymphoproliferative disorder[2] Bone marrow depression (severe courses), Aplastic anaemia, Eosinophilia, Neutropenia, Lymphadenopathy	Haemorrhages, Haematoma

Immune system disorders			Allergic reactions, Anaphylactic-type reaction, Fever, Chills		Immuno-suppression, Allergic vasculitis (severe toxic symptom), Hypogamma-globulinaemia	
Endocrine disorders			Diabetes mellitus			
Psychiatric disorders			Depression	Mood swings	Insomnia	
Nervous system disorders		Headache, Dizziness, Fatigue, Drowsiness	Convulsions, Vertigo, Confusion	Hemiparesis, Paresis	Acute aseptic meningitis with meningism (paralysis, vomiting), Taste changes (metallic taste), Irritation, Dysarthria, Aphasia, Lethargy, Pain, Muscular asthenia or paraesthesia/hypo aesthesia, Transient subtle cognitive dysfunction, Unusual cranial sensations, Psychoses, Cerebral oedema, Tinnitus	Encephalopathy/ Leukoencephalo pathy
Eye disorders				Severe visual disturbances	Retinopathy, Conjunctivitis, Blurred vision	
Cardiac disorders				Pericardial effusion, Pericarditis, Pericardial tamponade		
Vascular disorders			Nosebleed	Hypotension. Thromboemboli c reactions (including arterial and cerebral thrombosis, thrombophlebiti, deep leg vein thrombosis, retinal vein	Vasculitis	

				thrombosis, pulmonary embolism)		
Respiratory, thoracic and mediastinal disorders		Pneumonitis, Interstitial pneumonitis (can be fatal)	Pulmonary fibrosis	Respiratory paralysis, Bronchial asthma-like reactions such as cough, dyspnoea and pathological changes in lung function tests Pharyngitis (see section 4.4)	Pneumocystis jiroveci pneumonia and other lung infections, Chronic interstitial obstructive lung disease, Chronic obstructive pulmonary disease, Pleuritis, Dry cough, Pleural effusion	Epistaxis, Pulmonary alveolar haemorrhage*
Gastrointestinal disorders	Loss of appetite, Nausea, Vomiting, Abdominal pain, Inflammation and ulceration of mucosa of mouth and throat, Stomatitis, Dyspepsia	Anorexia, Diarrhoea	Ulceration and bleeding of gastrointestinal tract	Gingivitis, Glossitis, Gastrointestinal ulcerations and haemorrhage, Enteritis, Pharyngitis, Pancreatitis, Malabsorption Melaena	Haematemesis, Haematorrhoea, Toxic megacolon	
Hepatobiliary disorders	Increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin)		Hepatic steatosis, fibrosis and cirrhosis, Decrease in serum albumin	Hepatotoxicity, periportal fibrosis, liver cirrhosis, acute hepatitis, hepatic necrosis, fatty metamorphosis which may be fatal in chronic administration.	Acute liver degeneration, Liver failure, Reactivation of chronic hepatitis	Hepatitis and liver failure[4]
Skin and subcutaneous tissue disorders		Erythema, Exanthema, Pruritus,	Severe toxic manifestations: vasculitis and extensive herpetiform skin eruptions Stevens-Johnson's syndrome, Toxic Epidermal	Onycholysis, Acne, Bruising, Erythema multiforme, Cutaneous erythematous eruptions, Lesions of psoriasis may worsen with	Telangiectasis, Furunculosis, Ecchymoses, Acute paronychia, Hydradenitis	Skin exfoliation/Dermatitis exfoliative

			Necrolysis (Lyell's syndrome), Increased rheumatic nodules, Painful erosions of psoriatic plaque, Photosensitivity reactions, Increased skin pigmentation, Hair loss, Impaired wound healing, Urticaria	concomitant UV therapy, Radiation dermatitis and sunburn may be "recalled", Hyperpigmentation of the nails. Petechiae		
Musculoskeletal and connective tissue disorders			Osteoporosis, Arthralgia, Myalgia	Stress fracture	Osteoporosis including aseptic necrosis of the femoral head.	Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Nephropathy, Inflammation and ulceration of urinary bladder (possibly with haematuria), Dysuria	Renal failure, Oliguria, Anuria, Azotaemia	Proteinuria	
Reproductive system and breast disorders.			Vaginal inflammation and ulceration	Oligospermia, Menstrual disorders	Formation of defective oocytes or sperm cells, infertility. Vaginal bleeding, Gynaecomastia, Loss of libido, impotence, vaginal discharge	
General disorders and administration site conditions					Fever	Oedema

[1] can be reversible - see 4.4

[2] 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.

[3] has been reported for methotrexate used in rheumatologic and related indications

[4] see remarks on liver biopsy in section 4.4

Paediatric population

Frequency, type and severity of adverse reactions in children and adolescents are expected to be the same as in adults.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The symptoms following oral overdose predominantly affect the haematopoietic and gastrointestinal systems. Symptoms include leucocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and bleeding.

Leucovorin is a specific antidote for methotrexate and, following accidental overdosage, should be administered within one hour at a dosage equal to, or greater than, the methotrexate dose and dosing continued until serum levels of methotrexate are below 10-7 mol/L. It may be administered by i.v. bolus or infusion. Further doses may be required. The patient should be observed carefully and blood transfusions, renal dialysis (see below) and reverse barrier nursing may be necessary.

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. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser. Peritoneal dialysis has not been shown to improve methotrexate elimination.

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions. There are reports of deaths from sepsis, septic shock, renal failure and aplastic anaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antimetabolites, Folic acid analogues; ATC code: L01BA01

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamation of methotrexate caused by the folylpolyglutamylate enzyme, the duration of the cytotoxic effect of the drug substance in the cell increases.

Methotrexate is a phase-specific substance the main action of which is directed to the S-phase of cell mitosis. It acts generally most effectively on actively increasing tissues, such as malignant cells, bone marrow, fetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is higher than that of most normal cells, methotrexate can slow down the proliferation of malignant cells without causing, however, irreversible damage to normal tissue.

Calcium folinate is a folinic acid which is used to protect normal cells from the toxic effects of methotrexate. Calcium folinate enters the cell through a specific transport mechanism, is converted in the cell into active folates and reverses the inhibition of the precursor synthesis caused by the DNA and RNA.

5.2 Pharmacokinetic properties

The effect of orally administered methotrexate seems to be dependent on the size of the dose. Peak concentrations in serum are reached within 1–2 hours. Generally a dose of methotrexate of 30 mg/m^2 or less is absorbed rapidly and completely. The bioavailability of orally administered methotrexate is high (80–100%) at doses of 30 mg/m^2 or less. Saturation of the absorption starts at doses above 30 mg/m^2 and absorption at doses exceeding 80 mg/m^2 is incomplete.

The drug is actively transported across cell membranes and is bound as polyglutamate conjugates. The drug is widely distributed into body tissues with the highest concentrations in the kidneys, gallbladder, spleen, liver, skin, colon and small intestine. The drug may remain in the body for several months, particularly in the liver. As the drug penetrates ascetic fluid and effusions, these spaces may act as depots.

Data from a randomised trial in patients with juvenile rheumatoid arthritis (aged 2.8 to 15.1 years) indicated greater oral bioavailability of methotrexate in the fasting state. In children with JIA, the dose normalized area under the plasma concentration versus time-curve (AUC) of methotrexate increased with the age of the children and was lower than that found in adults. The dose normalized AUC of the metabolite 7-hydroxymethotrexate was not dependent on age.

The drug undergoes hepatic and intracellular metabolism to polyglutamated forms, which can be converted back to methotrexate by hydrolase enzymes. Small amounts of these active metabolites may be converted to 7-hydroxymethotrexate. The accumulation of this metabolite may become substantial following the administration of high doses. The clearance of methotrexate form the serum is reported to be triphasic and the terminal elimination half-life is within a range of 3 – 10 hours for patients receiving methotrexate for rheumatoid arthritis, psoriasis or who have received low-dose methotrexate antineoplastic therapy. In patients receiving high-

dose methotrexate, the elimination half-life is within the range between 8 and 15 hours. The drug is eliminated primarily in the urine by glomerular filtration and active tubular secretion. Approximately 41% of the dose is excreted unchanged in the urine within the first six hours, 90% within 24 hours. A minor part of the dose is excreted in the bile of which there is pronounced enterohepatic circulation.

Delayed drug clearance has been reported to be one of the major reasons for methotrexate toxicity. Excretion is impaired and accumulation occurs more rapidly in patients with impaired renal function, pleural effusions, or those with other "third-space" compartments (e.g. ascites).

Approximately 50% of the drug is bound to serum proteins and laboratory studies demonstrate that the drug may be displaced from plasma albumin by various compounds, including sulphonamides, salicylates, tetracyclines, chloramphenicol and phenytoin.

Methotrexate crosses the placental barrier and is distributed into breast milk**.**

5.3 Preclinical safety data

Chronic toxicity

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

Mutagenic and carcinogenic potential

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

Reproductive toxicology

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Methyl Parahydroxybenzoate E219

Sodium Ethyl Parahydroxybenzoate E215

Disodium Hydrogen Phosphate Dihydrate E339

Citric Acid Monohydrate E330

Sucralose E955

Raspberry Flavour (containing propylene glycol and sulphites)

Purified Water

6.2 Incompatibilities

None stated

6.3 Shelf life

18 months.
After first opening, the product may be stored for a maximum of 3 months.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate. Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Bottle: Amber (Type III glass)

Packs:

- 35ml, or 65ml, cartonned with an oral dosing device (LDPE body, white polystyrene plunger with a capacity of 10ml, major dosage graduation at every 1ml, minor dosage graduation at every 0.25ml) and a bottle adaptor (low density polyethylene).

Closure: HDPE, EPE wadded, child resistant closure. White HDPE cap with PE liner; child resistant and tamper evident

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Safe handling

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 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.

Women who are pregnant, planning to be or breastfeeding should not handle methotrexate.

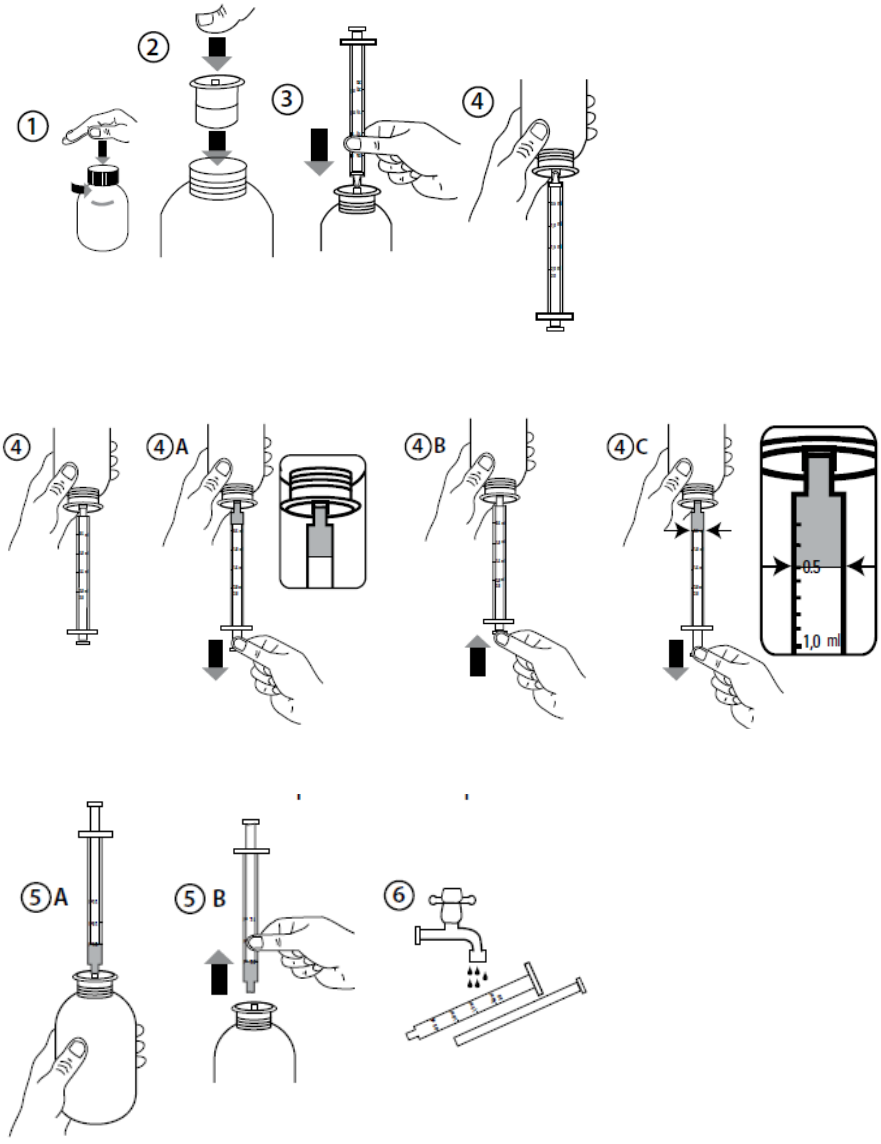
Parents / care givers and patients should be advised to keep methotrexate out of the reach and sight of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Keep the bottle tightly closed to protect the integrity of the product and minimise the risk of accidental spillage.

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

<u>Instructions for use of the syringe provided with the pack, or as directed by the healthcare professional:</u>

- Open the bottle: press the cap and turn it anticlockwise (Figure 1).
- Insert the syringe adaptor into the bottle neck (Figure 2).
- Take the syringe and put it in the adaptor opening (Figure 3).
- Turn the bottle upside down (Figure 4).
- Fill the syringe with a small amount of solution by pulling the piston down (Figure 4A). Then push the piston upward in order to remove any possible bubbles (Figure 4B). Finally, pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor. The top flat edge of the piston should be in line with the graduation mark you are measuring to (Figure 4C).
- Turn the bottle the right way up (Figure 5A).
- Remove the syringe from the adaptor (Figure 5B).
- Put the end of the syringe into your mouth and push the piston slowly back in to take the medicine. Alternatively, dispense the solution onto a spoon or into a small glass of water and take your medicine straight away.
- Once the dose has been swallowed, a glass of water should be drunk to remove any methotrexate residue from the oral cavity.
- Close the bottle with the plastic screw cap - leave the syringe adaptor in the bottle.
- Wash the syringe with warm ‘soapy’ water and rinse well. Hold the syringe under water and move the plunger up and down several times to make sure the inside of the syringe is clean. Let the syringe dry completely before you use that syringe again for dosing. Store the syringe in a hygienic place with the medicine. (Figure 6.)
- HANDS SHOULD BE WASHED THOROUGHLY with soap and warm water IMMEDIATELY after use.



7 MARKETING AUTHORISATION HOLDER

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LS11 9XE

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8 MARKETING AUTHORISATION NUMBER(S)

PL 00427/0233

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/01/2025

10 DATE OF REVISION OF THE TEXT

13/01/2025