Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg methotrexate.

Excipient with known effect:
Each tablet contains 50 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Methotrexate 10 mg: Yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10.00 mm ± 0.20 mm and breadth 5.00 mm ± 0.20 mm, with central breakline on one side and plain on other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate tablet is indicated in the treatment of:

- Active rheumatoid arthritis in adult patients.
- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy and active psoriatic arthritis in adults
- Maintenance therapy in acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.

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.

Posology

Rheumatological and dermatological diseases

Important warning with reference to the dosing of Methotrexate Tablets:
In the treatment of Rheumatological and dermatological diseases, Methotrexate Tablets **must be taken once a week.** Dosage errors in the use of Methotrexate Tablets (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

Methotrexate is given once weekly.

It must be explicitly pointed out to the patient that methotrexate is taken **only once a week**.

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

The dose and duration of treatment are determined individually on the basis of the patient's clinical picture and the tolerability of methotrexate. Treatment of active rheumatoid arthritis, severe psoriasis and severe psoriatic arthritis represents a long-term treatment.

A weekly dose of 25 mg should not be exceeded. Doses exceeding 20 mg/week can be associated with a substantial increase in toxicity, especially bone marrow depression.
Concurrent folic acid supplementation of 5 mg twice weekly (except on the day of administration) is indicated additionally.

Dosage in adult patients with Rheumatoid arthritis

The recommended initial dose is 7.5 - 15 mg methotrexate once weekly. Depending on the individual activity of the disease and tolerability by the patient, the dose may be increased gradually by 2.5 mg per week.
Response treatment can be expected after approximately 4-8 weeks.
After the desired treatment outcome is achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose.
Symptoms may return after treatment discontinuation.
*Dosage in adults with severe forms of psoriasis and adult patients with psoriatic arthritis*It is recommended that a test dose of 2.5-5 mg be administered one week prior to initiation of therapy, in order to detect early occurring adverse reactions. If, one week later, appropriate laboratory tests are normal, treatment may be initiated. The recommended initial dose is 7.5 mg methotrexate once weekly. The dose should be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. The usual dose is 10 mg–25 mg taken once weekly. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression.
Response to treatment can generally be expected after approximately 4-8 weeks. After the desired treatment outcome is achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose.
Oncology
Dosage in acute Lymphoblastic Leukaemia

Low-dose methotrexate is used in the maintenance treatment of ALL in children aged 3 years and over, adolescents and adults within complex protocols in combination with other cytostatic medicinal products. Treatment should follow current therapy protocols.

Common accepted single doses lie in the range of 20-40 mg/m² body surface area, **once weekly**.

If methotrexate is administered in combination with chemotherapy regimens, the dosage should take into consideration any overlapping toxicity of the other medicinal product components.

Higher dosages should be given parenterally.

Paediatric population
Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children (see section 4.4).

Doses are usually based on the patient's BSA and maintenance treatment represents a long-term treatment.

Special populations
Renal impairment

Methotrexate should be used with caution in patients with impaired renal function (see section 4.4). The dose should be adjusted as follows for patients with rheumatoid arthritis, psoriasis and psoriatic arthritis. For the oncology indication recommendations in published protocols should also apply:

Creatinine clearance (ml/min) Dose
> 60 100 %
30 – 59 50 %
< 30 Methotrexate must not be used

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).

Paediatric population
Use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this patient group

Elderly

Dose reduction should be considered in elderly patients (65 years and over) due to reduced liver and kidney function as well as low folic acid reserves which occur with increased age. In addition, close monitoring of patients for possible early signs of toxicity is recommended (see sections 4.4, 4.5, 4.8 and 5.2).

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.

Method of administration
Oral

4.3 Contraindications

- Hypersensitivity to the active substanceor to any of the excipients listed in section 6.1
- Hepatic impairment (bilirubin levels are >5 mg/dl [85.5 µmol/l], see section 4.2)
- Alcohol abuse
- Severe renal impairment (creatinine clearance less than 30 ml/min, see section 4.2).
- Pre-existing blood disorders, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Immunodeficiency
- 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)
- 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 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 intakes.
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 a 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 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.

Recommended examinations and safety measures
Before beginning treatment or resuming treatment after a recovery 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, tuberculosis and hepatitis B and C should be excluded.

During treatment
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. 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.
- 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.
- 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.

- Respiratory tract examination - patients must be monitored for symptoms of a lung function disorder and lung function tests performed if necessary. Lung-related symptoms (particularly a dry, non-productive cough) or non-specific pneumonitis that occurs during treatment with methotrexate can be a sign of potentially dangerous damage and require the discontinuation of treatment and careful monitoring. Although the clinical presentation is variable, patients with methotrexate-induced lung diseases typically suffer from fever, cough, dyspnoea or hypoxaemia. A chest X-ray must be taken in order to be able to exclude an infection. Acute or chronic interstitial pneumonia, often in association with blood eosinophilia, may occur and deaths have been reported. Patients should be informed of the risks of pneumonia and advised to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Methotrexate should be discontinued in patients with pulmonary symptoms and an immediate examination (including chest X-ray) should be performed to exclude infection and tumours. If methotrexate-induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Pulmonary symptoms require a 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.

Renal impairment and patients at risk of renal impairment

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. (See renal function monitoring)

Immune system
Due to its effect on the immune system, methotrexate may impair the response to vaccinations and affect the results of immunological tests. Concurrent vaccination using live vaccines should not be given.

Malignant lymphomas
Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. If the lymphomas fail to regress spontaneously, cytotoxic treatment must be initiated.

Pleural effusions or ascites
Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 4.2).

Conditions that cause dehydration such as vomiting, diarrhoea or stomatitis

Conditions that cause dehydration such as vomiting, diarrhoea or stomatitis can increase toxicity as a result of raised active substance levels. In this case, treatment with methotrexate must be discontinued until the symptoms have disappeared.

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.

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.

Vitamin products
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate (see sections 4.2 and 4.5).

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

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.

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.

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of an interaction between NSAIDs and methotrexate should be considered in patients with a low methotrexate dose, particularly in the case of impaired kidney function. 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. Animal studies showed that the administration of NSAIDs including salicylic acid resulted in reduced tubular methotrexate secretion and accordingly potentiated its toxic effects. However, in clinical trials in which NSAIDs and salicylic acid were administered adjuvantly to patients with rheumatoid arthritis, no increase in adverse reactions was observed. Treatment of rheumatoid arthritis with such medicinal products can be continued during therapy with low-dose methotrexate, but only under close medical supervision.
Patients taking potentially hepatotoxic medicinal products during treatment with methotrexate (e.g. leflunomide, azathioprine, sulfasalazine and retinoids) should be monitored closely for increased hepatotoxicity. 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 (e.g. metamizole) increases the likelihood of severe haematotoxic adverse reactions to methotrexate.

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

Salicylates, phenylbutazone, diphenylhydantoin (= phenytoin), barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulphonamides, thiazide diuretics, oral hypoglycaemics, doxorubicin and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability and hence toxicity (indirect dose increase). Probenecid and weak organic acids can also reduce the tubular secretion of methotrexate and thus likewise cause an indirect increase in dose.

Antibiotics such as penicillins, glycopeptides, sulphonamides, ciprofloxacin and cefalotin can in individual cases reduce the renal clearance of methotrexate, so that increased serum methotrexate concentrations can occur, accompanied by haematological and gastrointestinal toxicity.
Oral antibiotics, such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may reduce intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting intestinalflora or suppressing bacterial.

In the event of (prior) treatment with medicinal products that can have adverse reactions on bone marrow (e.g. sulphonamides, trimethoprim/sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of haematopoietic disorders must be considered.

Concomitant therapy with medicinal products that can cause folic acid deficiency (e.g. sulphonamides, trimethoprim/sulphamethoxazole) can result in increased methotrexate toxicity. Accordingly, particular caution should be exercised in patients with pre-existing folic acid deficiency.

Conversely, co-administration of medicinal products containing folinic acid or vitamin preparations containing folic acid or derivatives may impair the efficacy of 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.

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

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.

Co-administration of proton pump inhibitors such as omeprazole or pantoprazole can result in interactions: co-administration of methotrexate and omeprazole has resulted in delayed renal elimination of methotrexate. In one case in which methotrexate was combined with pantoprazole, renal elimination of the metabolite 7-hydroxymethotrexate was inhibited and myalgia and shivering occurred.

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

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.

Combination therapy with methotrexate and leflunomide may increase the risk for pancytopenia.
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.

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

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

Radiotherapy during the use of methotrexate can increase the risk for soft tissue or bone necrosis.
Methotrexate can reduce the clearance of theophylline. During concomitant therapy with methotrexate, therefore, serum theophylline levels should be monitored.

Combined administration of mercaptopurine and methotrexate can increase the bioavailability of mercaptopurine, possibly as a result of inhibition of the metabolism of mercaptopurine.

In view of its possible effects on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to assess the immune reaction). During methotrexate therapy, concurrent vaccination with live vaccines should be avoided (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and 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 lowdose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

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

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).

Breast-feeding

As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see section 4.3). Breast-feeding is therefore to be stopped prior to treatment.

4.7 Effects on ability to drive and use machines

Methotrexate has moderate influence on the ability to drive and use machines, since central nervous system disorders such as tiredness, dizzy spells or drowsiness can occur during treatment.

4.8 Undesirable effects

Summary of the safety profile
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.

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.

The occurrence and severity of adverse reactions depend on dosage level and frequency of administration of methotrexate. However, as severe adverse reactions may occur even at low doses, it is essential for the treating physician to monitor patients closely (see section 4.4).

Most adverse reactions are reversible if they are detected early. If such adverse reactions occur, the dose should either be reduced or treatment discontinued and appropriate countermeasures taken (see section 4.9). Methotrexate therapy should only be resumed with particular caution, after careful consideration of the need for treatment and with increased vigilance for the possible recurrence of toxicity..

The frequencies of the adverse reactions are classified as follows:
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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Very	Common	Uncommon	Rare	Very rare	Not known	

	Common						
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Lymphoma[1]				
Blood and lymphatic system disorders		Leukopenia, Thrombo-cytopenia, Anaemia	Pancytopenia, Agranulocytosis, Haematopoietic disorders	Megaloblastic anaemia	Bone marrow depression (severe courses), Aplastic anaemia, Lymphoproliferative disorder2, Eosinophilia, Neutropenia, Lymphadenopathy	Haemorrhages	
Nervous system disorders		Headache, Fatigue, Drowsiness	Convulsions, Vertigo, Confusion	Hemiparesis, Paresis	Cerebral oedema, Acute aseptic meningitis with meningism (paralysis, vomiting), Lethargy, Transient subtle cognitive dysfunction, Psychoses, Aphasia, Pain, Muscular asthenia or paraesthesia/ hypoaesthesia,, Taste changes (metallic taste), Irritation, Dysarthria, Unusual cranial sensations, Tinnitus	Encephalop-athy/ Leukoenceph-alopathy	
Eye disorders				Severe visual disturbances	Retinopathy, Conjunctivitis		
Cardiac disorders				Pericarditis, Pericardial effusion, Pericardial tamponade			
Vascular disorders				Thromboembolic reactions (including arterial and cerebral			

				thrombosis, thrombophlebitis, deep leg vein thrombosis, retinal vein thrombosis, pulmonary embolism), Hypotension			
Respiratory, thoracic and mediastinal disorders		Interstitial alveolitis/ pneumonia (can be fatal)	Pulmonary fibrosis	Respiratory paralysis, Bronchial asthma-like reactions such as cough, dyspnoea and pathological changes in lung function tests, Pharyngitis	Pneumocystis jiroveci pneumonia and other lung infections, Chronic obstructive pulmonary disease, Pleural effusion	Pulmonary alveolar haemorrhage3	
Gastrointestinal disorders[3]	Loss of appetite, Nausea, Vomiting, Abdominal pain, Inflammation and ulceration of mucosa of mouth and throat, Stomatitis, Dyspepsia	Diarrhoea	Ulceration and bleeding of gastrointestinal tract	Pancreatitis, Enteritis, Malabsorption, Melaena, Gingivitis	Toxic megacolon, Haematemesis		
Hepatobiliary disorders	Increase in liver-related enzymes		Hepatic steatosis, fibrosis and	Acute hepatitis and	Acute liver degeneration, Liver failure, Reactivation	Hepatitis and liver failure4	

	(ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin)		cirrhosis, Decrease in serum albumin	hepato toxicity	of chronic hepatitis,		
Skin and subcutaneous tissue disorders		Erythema, Exanthema, Pruritus	Severe toxic manifestations: vasculitis, herpetiform skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), Increased rheumatic nodules, Painful erosions of psoriatic plaque, Photosensitivity, Increased skin pigmentation, Hair loss, Impaired wound healing, Urticaria	Increased nail pigment changes, Onycholysis, Acne, Petechiae, Bruising, Erythema multiforme, Cutaneous erythematous eruptions, Lesions of psoriasis may worsen with concomitant UV therapy, Radiation dermatitis and sunburn may be "recalled"	Acute paronychia, Furunculosis, Telangiectasis, Hidradenitis	Skin exfoliation/Dermatitis exfoliative	
Musculoskeletal and connective tissue disorders			Osteoporosis, Arthralgia, Myalgia,	Stress fracture		Osteonecrosis of jaw (secondary to lymphoprolifer-ative 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 dysfunction	Infertility, Loss of libido,Impotence, Vaginal discharge, Gynaecomastia		
Infections and infestations		Infections.	Opportunistic infections (sometimes fatal).	Herpes zoster.	Sepsis Cytomegalovirus-induced infections.	Nocardiosis, Histoplasma and cryptococcus mycosis, Disseminated herpes simplex	
Immune system disorders			Allergic reactions, Anaphylactic shock, Fever, Chills		Immuno-suppression, Allergic vasculitis (severe toxic symptom), Hypogamma-globulinaemia		
Endocrine disorders				Diabetes mellitus.			
Psychiatric disorders			Depression	Mood swings	Insomnia		
Metabolism and nutrition disorders			Diabetes mellitus				
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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of 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.
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 hematological and gastrointestinal reactions.
There are reports of deaths from sepsis, septic shock, renal failure and aplastic anaemia.
Therapeutic management of overdose

Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate. In the event of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within 1 hour, and dosing continued until serum level of methotrexate are below 10^{-7} mol/L.

In the event of a massive overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve the elimination of methotrexate. Effective clearance of methotrexate is reported to be achieved with acute intermittent haemodialysis using a high-flux dialyser.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, ATC code: L04AX03

Mechanismofaction

Methotrexate is a folic acid antagonist that, as an antimetabolite, belongs to the class of cytotoxic active substances. It acts by competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.

It has not yet been possible to date to clarify whether the efficacy of methotrexate in the management of psoriasis, psoriatic arthritis and chronic polyarthritis is due either to an anti-inflammatory or immunosuppressive effect, or to what extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to this effect.

Highly proliferating tissue such as malignant cells, bone marrow, foetal cells, skin epithelium and mucosa is generally more sensitive to this effect of methotrexate. Cell proliferation is usually greater in malignant tumours than in normal tissue and methotrexate can therefore exert a sustained effect on malignant growth without causing irreversible damage to normal tissue.

In psoriasis, cell proliferation of the epithelium is markedly increased compared with normal skin.
This difference in cell proliferation rate is the starting point for the use of methotrexate in particularly severe, generalised, treatment-resistant psoriasis and psoriatic arthritis..

5.2 Pharmacokinetic properties

Absorption
After oral administration, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m2 to 80 mg/m2 body surface area), the mean bioavailability of methotrexate is approximately 70%, but considerable inter- and intra-individual variations are possible (25-100%). Peak serum concentrations are attained within 1-2 hours.

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.

Distribution
Methotrexate is approximately 50% bound to serum proteins. After distribution, it collects predominantly in the liver, kidneys and spleen in the form of polyglutamates, which can be retained for weeks or months.

The mean terminal half-life is 6-7 hours and demonstrates considerable variations (3-17 hours). The half-life may be prolonged up to four-fold in patients with a third distribution compartment (pleural effusion, ascites).

Biotransformation
Approximately 10% of the administered methotrexate dose is metabolised in the liver. The main metabolite is 7-hydroxymethotrexate.

Elimination
Excretion occurs predominantly in the unchanged form by glomerular filtration and active secretion in the proximal tubule via the kidneys.

Approximately 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate is eliminated in the bile. There is a pronounced enterohepatic circulation.

Elimination in patients with impaired renal function is markedly delayed. Impaired elimination in patients with hepatic impairment is not known at present.
Methotrexate crosses the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity studies in mice, rats and dogs, toxic effects were seen in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

Mutagenic and carcinogenic potential
Long-term studies in rats, mice and hamsters revealed no evidence of a tumorigenic potential of methotrexate. Methotrexate induces gene and chromosomal mutations in vitro and in vivo. There is a suspected mutagenic effect in humans.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous calcium hydrogen phosphate
Lactose monohydrate
Sodium starch glycolate (Type A)
Cellulose, microcrystalline
Talc
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Blister: Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister: Amber coloured PVC film and aluminium blister foil.

Pack sizes:
Blister pack: 10 tablets, 12 tablets, 15 tablets, 20 tablets, 24 tablets, 25 tablets, 28 tablets, 30 tablets, 50 tablets or 100 tablets

PVC/Alu perforated unit dose blister in pack-sizes of 10x1, 12x1, 15x1, 20x1 , 24x1 , 25x1, 28x1, 30x1,50x1 & 100 x1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Proper procedures for safe handling of cytotoxic agents should be administered. Disposable gloves should be used when handling methotrexate tablets. Pregnant women should avoid handling methotrexate tablets, if possible.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/062/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st July 2016
Day of last renewal: 30th June 2021

10 DATE OF REVISION OF THE TEXT

May 2023