SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate Orion 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methotrexate disodium equivalent to 10 mg methotrexate (anhydrous).

Excipient with known effect: 311.2 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Yellow, capsule-shaped, convex, uncoated, tablet, engraved with ORN 59 on one side and score on the other side, length of 14 mm and width of 6 mm.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Antirheumatic:* Active rheumatoid arthritis in adult patients
- *Antipsoriatic:* Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients
- *Cytostatic*: Maintenance treatment of 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.

Important warning with reference to the dosing of Methotrexate Orion (methotrexate):

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

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

It must be explicitly pointed out to the patient that for the therapy of rheumatic diseases, psoriasis or severe psoriatic arthritis methotrexate is administered **only once a week.**

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

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

Rheumatoid arthritis

The usual dose is 7.5 - 15 mg once weekly. The dose may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 25 mg. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Thereafter the dose should be reduced to the lowest possible effective dose which in most cases is achieved within 6 weeks.

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 usual dose is 7.5–15 mg taken once weekly. As necessary, the total weekly dose can be increased up to 25 mg. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which in most cases is achieved within 4 to 8 weeks.

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 during therapy as detailed in section 4.4 under “Recommended examinations and safety measures”. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged.

Cytostatic

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 and are usually given 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 valid therapy protocols for children. Doses are usually based on the patient's body surface area and maintenance treatment represents a long-term treatment.

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

Special populations

Use in elderly patients

Methotrexate should be used with extreme caution in elderly patients, a dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Patients with renal impairment:

Methotrexate should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). The dose should be adjusted as follows:

Dosage recommendations

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

Patients with hepatic impairment:

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. Methotrexate is contraindicated in patients with significantly impaired hepatic function, see sections 4.3 and 4.4.

Use in patient with a third distribution space (pleural effusions, ascites)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see section 5.2 and 4.4).

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

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

4.3 Contraindications

- Hypersensitivity to methotrexate or to any of the excipients listed in section 6.1
- Significantly impaired hepatic function
- Alcoholism
- Significantly impaired renal function
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Severe acute or chronic infections and immunodeficiency syndromes
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- 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

Dosing in the treatment of rheumatoid arthritis, psoriasis and severe psoriatic arthritis:

The patients should be informed clearly that in the treatment of rheumatoid arthritis, psoriasis or severe psoriatic arthritis the administration is once weekly.

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

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

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

Warnings

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy.

Concomitant administration of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drug, e.g. leflunomide) is not advisable.

Due to the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and be under constant supervision. 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.

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 /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 (see sections 4.2 and 4.3).

Fertility and reproduction

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.

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* - particular attention should be given to the appearance of liver toxicity. 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/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 (see section 4.5).

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).

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.

Skin toxicity
Epidermal necrosis, mostly accompanied by leukopenia, thrombocytopenia and mucosal lesions, has been reported with methotrexate treatment (see section 4.8). This cutaneous reaction may clinically mimic Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. If signs and symptoms suggestive of these reactions appear, methotrexate should be withdrawn immediately, and appropriate treatment should be initiated. Intervention with folinic acid has been described for epidermal necrosis. Methotrexate should not be reintroduced unless SJS and TEN have been excluded.

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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Hepatotoxic agents

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

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

Hematotoxic agents

Hematotoxic medicinal products should not be taken during treatment with methotrexate. If concomitant administration cannot be avoided, patients should be monitored closely for signs and symptoms of hematotoxicity including close monitoring of blood count and platelets (see section 4.4).

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

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

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

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

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis 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.

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

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate (see section 4.4).

Ciclosporin

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

Pharmacokinetic interactions

Interactions which may increase methotrexate levels

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

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

Methotrexate is plasma protein bound and certain drugs such as oral hypoglycaemics, thiazide diuretics, sulfonamides, phenytoin, barbiturates, tranquilisers, oral contraceptives, amidopyrine derivatives, doxorubicin, p-aminobenzoic acid, some antibiotics such as penicillins (e.g. amoxicillin), tetracyclines, chloramphenicol decrease this binding, which can lead to increased toxicity when used concurrently.

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

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

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

Penicillins (e.g. amoxicillin), glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastrointestinal toxicity may occur.

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

Interactions which may reduce methotrexate levels

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

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

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

Methotrexate effects on other medicinal products

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

One should be aware of pharmacokinetic interactions between methotrexate and 5-fluorouracil (increased t½ of 5--fluorouracil). If coadministration is necessary, patient should be monitored for 5-fluorouracil toxicity and dose adjustments should be considered if necessary.

Theophylline and caffeine

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

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

Infection risk and vaccinations

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections (see section 4.3). On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see sections 4.3 and 4.4).

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

Radiotherapy

Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in females

Women must not get pregnant during methotrexate therapy 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.

Breastfeeding

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.

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 may be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Central nervous system symptoms, such as fatigue and dizziness, can occur during treatment with methotrexate which have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Generally, the frequency and severity of adverse reactions are dependent of the size of the dose, the dosing frequency, the method of administration and the duration of exposure.

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 observed (very common) adverse reactions of methotrexate include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite) and abnormal liver function tests (e.g. increased Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently occurring (common) adverse reactions are leukopenia, anaemia, thrombocytopenia, 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).

Tabulated list of adverse reactions

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).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Infections	Opportunistic infections	Herpes zoster Sepsis Reactivation of inactive chronic infection	*Pneumocystis jiroveci* pneumonia	Sepsis resulting in death
Neoplasms benign,malignant and unspecified (including cysts and polyps)			Lymphoma[1]			
Blood and lymphatic system disorders		Leukopenia Thrombocytopenia Anaemia	Bone marrow depression Pancytopenia Agranulocytosis Haematopoietic disorders	Megaloblastic anaemia	Hypogammaglobulinaemia Aplastic anaemia Lymphoproliferative disorder Neutropenia Lymphadeno	Eosinophilia

	Very common	Common	Uncommon	Rare	Very rare	Not known
					pathy	
Immune system disorders			Anaphylactic-type reaction Allergic reactions Anaphylactic shock		Immunosuppression	
Metabolism and nutrition disorders			Diabetes mellitus			
Psychiatric disorders			Depression Confusion	Mood swings	Insomnia	
Nervous system disorders		Headache Dizziness Fatigue Drowsiness	Convulsions Vertigo	Hemiparesis Paresis	Cerebral oedema Acute aseptic meningitis with meningism (paralysis, vomiting) Irritation Dysarthria Aphasia Lethargy Transient subtle cognitive dysfunction Dysarthria Unusual cranial sensations Pain, muscular asthenia Paraesthesia/ hypoaesthesia Changes in sense of taste (metallic taste)	Encephalopathy/Leucoencephalopathy
Eye				Severe visual	Conjunctiviti	

	Very common	Common	Uncommon	Rare	Very rare	Not known
disorders				disturbances	s Impaired vision Retinopathy	
Cardiac disorders				Pericardial effusion Pericarditis Pericardial tamponade		
Vascular disorders			Nosebleed	Hypotension Thromboembolism	Vasculitis	
Respiratory, thoracic and mediastinal disorders		Interstitial alveolitis/pneumonitis (can be fatal)	Interstitial fibrosis	Respiratory paralysis Dyspnoea Pharyngitis[2] Bronchial asthma	Chronic interstitial obstructive lung disease Pleuritis Dry cough Pleural effusion	Alveolitis Pulmonary alveolar haemorrhage[3]
Gastrointestinal disorders[4]	Stomatitis Anorexia Nausea Vomiting Dyspepsia Abdominal pain	Oral ulcers Diarrhoea	Gastrointestinal ulcerations and bleeding	Pancreatitis Gingivitis Enteritis Melaena	Toxic megacolon Haematemesis	
Hepatobiliary disorders	Elevated alkaline phosphatase and bilirubin Elevated transaminase concentrations (ALAT, ASAT)		Cirrhosis, Fibrosis and fatty degeneration of the liver Decrease in serum albumin	Hepatotoxicity Acute hepatitis	Reactivation of chronic hepatitis Hepatic failure	
Skin and subcutaneous tissue disorders		Erythematous rash Exanthema Pruritus Alopecia	Allergic vasculitis Herpetiform eruptions of the skin Stevens-Johnson´s syndrome	Increased nail pigment changes Acne Petechiae Depigmentation	Acute paronychia Telangiectasia Furunculosis Ecchymoses Hidradenitis	Skin exfoliation / dermatitis exfoliative Epidermal necrosis

	Very common	Common	Uncommon	Rare	Very rare	Not known
			Toxic epidermal necrolysis Increase in rheumatoid nodules Increased skin pigmentation Impaired wound healing Photosensitivity reactions	Urticaria Erythema multiforme Painful damage to psoriatic lesion Skin ulceration Onycholysis		
Musculoskeletal and connective tissue disorders			Osteoporosis Arthralgia Myalgia	Stress fracture		Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Disturbed micturition Inflammation and ulceration of the urinary bladder (possibly with hematuria) Renal insufficiency Nephropathy	Oliguria Anuria Electrolyte disturbances	Dysuria Azotaemia Cystitis Haematuria Proteinuria	
Reproductive system and breast disorders			Vaginal inflammation and ulceration	Impotence Menstrual disorders	Loss of libido Formation of defective oocytes or sperm cells Transient oligospermia, infertility Vaginal discharge Vaginal bleeding Gynaecomastia	

	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions			Chills		Fever	Asthenia Oedema
Injury, poisoning and procedural complications						Increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy, Psoriatic lesions may get worse from simultaneous exposure to methotrexate and ultraviolet radiation.

[1] Can be reversible (see 4.4).

[2] See section 4.4.

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

[4] Gastrointestinal severe adverse reactions require often dose reduction. Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Symptoms:
Toxicity of methotrexate mainly affects the haematopoietic and gastrointestinal systems. Symptoms include leukopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.
There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

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.

Treatment:
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.
In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour
Observation of serum methotrexate concentrations is relevant in determining the right dose of calcium folinate and the duration of the therapy.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups:

Other immunosuppressants, ATC code: L04AX03

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid leading to decreased cellular proliferation. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamylation of methotrexate caused by the folylpolyglutamate synthetase 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 proliferating tissues, such as malignant cells, bone marrow, foetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is faster than that of most normal cells, methotrexate can slow down the proliferation of malignant cells without causing 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 synthesis of precursors of DNA and RNA.

5.2 Pharmacokinetic properties

Absorption

The effect of orally administered methotrexate is 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. At doses above 30 mg/m^2 absorption becomes nonlinear and absorption at doses exceeding 80 mg/m^2 is incomplete.

Distribution

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

Biotransformation

Approx. 10 % of the administered methotrexate dose is metabolised in the liver. The principle metabolite is 7-hydroxymethotrexate.

Elimination

Excretion takes place, mainly in unchanged form, primarily via glomerular filtration and active secretion in the proximal tubule.

Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary with pronounced enterohepatic circulation

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

Special populations

In the case of renal insufficiency, elimination is delayed significantly.

5.3 Preclinical safety data

Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity. Animal studies show that methotrexate impairs fertility, and is embryo- and foetotoxic. Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys no malformations occurred. Methotrexate is mutagenic *in vivo* and *in vitro*. There is evidence that methotrexate causes cromosomal aberrations in animal cells and in human bone marrow cells, but the clinical significance of these findings has not been established. Rodent carcinogenicity studies do not indicate an increased incidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Cellulose, microcrystalline

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/Al blister pack.

10 mg: 4, 8, 10, 12, 16, 20, 24, 30, 36, 40, 48, 50, 60, 100 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Proper procedures for safe handling of cytotoxic agents should be administered. Anyone handling methotrexate should wash their hands before and after administering a dose. Disposable gloves should be used when handling methotrexate tablets. Pregnant, planning to be or breast-feeding women should avoid handling methotrexate tablets, if possible.

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

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

Accidental ingestion can be lethal for children.

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

7 MARKETING AUTHORISATION HOLDER

Orion Corporation

Orionintie 1

FI-02200 Espoo

Finland

8 MARKETING AUTHORISATION NUMBER(S)

PA 1327/019/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st October 2016

Date of last renewal: 6th July 2021

10 DATE OF REVISION OF THE TEXT

2026-09-02