SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nordimet 12.5 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 25 mg of methotrexate.

Nordimet 12.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 12.5 mg methotrexate in 0.5 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, yellow solution with a pH of 8.0-9.0 and an osmolality of approximately 300 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nordimet is indicated for the treatment of:
- active rheumatoid arthritis in adult patients,
- polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, psoralens and ultraviolet A (PUVA), and retinoids, and severe psoriatic arthritis in adult patients,
- Induction of remission in moderate steroid-dependent Crohn's disease in adult patients, in combination with corticosteroids and for maintenance of remission, as monotherapy, in patients who have responded to methotrexate.

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.

Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Nordimet should be performed under direct medical supervision.

Important warning about the dosage of Nordimet
In the treatment of rheumatoid arthritis, active juvenile idiopathic arthritis, psoriasis, psoriatic arthritis and Crohn's disease requiring dosing once a week. Nordimet **must only be used once a week.** Dosage errors in the use of Nordimet can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

When switching from oral use to subcutaneous use, a reduction in the dose may be required, due to the variable bioavailability of methotrexate after oral administration.

Folic acid or folinic acid supplementation may be considered in accordance with current therapeutic guidelines.

The overall duration of treatment is decided by the doctor.

Posology

Dosage in adult patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. Depending on the individual activity of the disease and patient tolerability, the initial dose may be increased. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression**.** Response to treatment can be expected after approximately 4-8 weeks. Once the desired therapeutic result has been achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose. Symptoms may return after treatment discontinuation.

Methotrexate treatment of rheumatoid arthritis represents long-term treatment.

Dosage in patients with psoriasis vulgaris and psoriatic arthritis
It is recommended that a test dose of 5-10 mg be administered subcutaneously one week prior to initiation of therapy, in order to detect idiosyncratic adverse effects. The recommended initial dose is 7.5 mg methotrexate once weekly. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2-6 weeks. Depending on the clinical picture and the changes of laboratory parameters, the therapy is then continued or discontinued.

Once the desired therapeutic result has been achieved, dose should be reduced gradually to the lowest possible effective maintenance dose. In a few exceptional cases a higher dose than 25 mg might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Methotrexate treatment of severe psoriasis vulgaris and psoriatic arthritis represents long-term treatment.

Dosage in adult patients with Crohn's disease:

Induction treatment
25 mg/week administered subcutaneously.
Once patients have adequately responded to combination therapy, the corticosteroids should be tapered. Response to treatment can be expected after 8 to 12 weeks.

Maintenance treatment
15 mg/week administered subcutaneously, as monotherapy, if the patient has entered remission.

Special populations

Elderly
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age (see sections 4.4, 4.5, 4.8 and 5.2).

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:

Creatinine clearance (ml/min)	Dose
≥ 60	100 %

30-59	50 %
< 30	Nordimet 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 when caused by alcohol. Methotrexate is contraindicated if bilirubin values are > 5 mg/dl (85.5 µmol/L) (see section 4.3).

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

Paediatric population

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10-15 mg/m² body surface area (BSA) per week.
In therapy-refractory cases the weekly dose may be increased up to 20 mg/m² BSA per week.
However, an increased monitoring frequency is indicated if the dose is increased. Parenteral administration is limited to subcutaneous injection. Patients with JIA should always be referred to a rheumatology unit specializing in the treatment of children/adolescents.

The safety and efficacy of Nordimet in children < 3 years of age have not been established (see section 4.4). No data available.

Method of administration
It must be explicitly pointed out to the patient that Nordimet is applied only once a week. It is recommended to specify a certain day of the week as “day for injection”.

Nordimet is for subcutaneous use (see section 6.6.).

The medicinal product is for single use only. The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.
Any contact of methotrexate with skin and mucosa is to be avoided. In case of contamination, the affected parts are to be rinsed immediately with plenty of water (see section 6.6).

Please refer to the package leaflet for instructions on how to use the pre-filled pen or pre-filled syringe.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic impairment if serum if bilirubin is > 5 mg/dl (85.5 µmol/l) (see section 4.2).
- Alcohol abuse.
- Severe renal impairment (creatinine clearance less than 30 ml/min) (see sections 4.2 and 4.4).
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia.
- Immunodeficiency.
- Serious, acute or chronic infections such as tuberculosis and HIV.
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- Pregnancy and breast-feeding (see section 4.6).
- Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly advised that the therapy is to be administered once a week, and not every

day. Incorrect administration of methotrexate can lead to severe, including potentially lethal adverse reactions. Healthcare professionals and patients should be clearly instructed.

Patients receiving therapy should be appropriately monitored, so that signs of possible toxic effects or adverse reactions can be recognised and assessed without delay. Hence, methotrexate should be only administered by, or under the supervision of, doctors whose knowledge and experience include the use of antimetabolite therapy.

Due to the risk of severe or even fatal toxic reactions, patients should be thoroughly informed by the doctor about the risks (including early signs and symptoms of toxicity) and recommended safety measures. They are to be informed about the necessity to immediately consult the physician if symptoms of intoxication occur, as well as about the subsequent necessary monitoring of symptoms of intoxication (including regular laboratory tests).

Doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Skin and mucosal contact with methotrexate is to be avoided. In the case of contamination, the parts concerned should be rinsed with plenty of water.

Fertility and reproduction

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

Teratogenicity – reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Nordimet is used. If women of child bearing potential 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 initiating therapy or upon resuming therapy after a rest period
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest X-ray and renal function tests must be conducted. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy
The tests below must be conducted every week during the first two weeks, then every two weeks for the next month; afterwards, depending on leukocyte count and stability of the patient, at least once monthly during the next six months and at least every three months thereafter.
Increased monitoring frequency should also be considered when increasing the dose. Particularly elderly patients should be examined for early signs of toxicity in short intervals.

Examination of the oral cavity and throat for mucosal change.

Complete blood count with differential blood count and platelets
Haematopoietic suppression induced by methotrexate may occur abruptly and at apparently safe doses. In the event of any significant drop in leukocytes or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all

signs and symptoms suggestive of infection. In patients concomitantly taking haematotoxic medicinal products (e.g. leflunomide), the 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, or if these develop during therapy.

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-related 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 drugsor 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
Renal function should be monitored via renal function tests and urinanalysis (see sections 4.2 and 4.3). If serum creatinine is increased, the dose should be reduced. As methotrexate is predominantly excreted via the renal route, increased concentrations can be expected in cases of renal impairment, which may result in severe adverse reactions. In cases of possible renal impairment (e.g. in elderly patients), closer monitoring is required. This particularly applies to the co-administration of medicinal products which affect methotrexate excretion, cause kidney damage (e.g. NSAIDs) or can potentially lead to haematopoietic disorders. In patients with impaired renal function, concomitant administration of NSAIDs is not recommended. Dehydration may also potentiate the toxicity of methotrexate.

Assessment of respiratory system
Questioning the patient with regard to possible pulmonary dysfunctions, if necessary, lung function test. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

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

Methotrexate should be discontinued in patients with pulmonary symptoms and a thorough

investigation (including chest x-ray) should be made to exclude infection and tumours. If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Pulmonary diseases induced by methotrexate were not always completely reversible.

Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pulmonary diseases induced by methotrexate, like pneumonitis, can occur acutely at any time of therapy, they were not always completely reversible and have been reported already at all doses (inclusive low doses of 7.5 mg/week).

During methotrexate therapy, opportunistic infection can occur including pneumocystis jiroveci pneumonia, which may take a lethal course. If a patient presents with pulmonary symptoms, the possibility of pneumocystis jiroveci pneumonia should be taken into account.

Special caution is required in patients with impaired pulmonary function.

General safety measures
Methotrexate may, due to its effect on the immune system, impair the response to vaccinations and interfere with the result of immunological tests. Concurrent vaccination using live vaccines must not be carried out.

Particular caution should be exercised in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation.

Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

In patients with pathological accumulation of liquid in body cavities ("third space"), such as ascites or pleural effusions, the plasma elimination half-life of methotrexate is prolonged. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.

Conditions leading to dehydration such as emesis, diarrhoea or stomatitis, can increase the toxicity of methotrexate due to elevated levels of the active substance. In these cases use of methotrexate should be interrupted until the symptoms cease.

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
If haematemesis, black discoloration of the stool or blood in stool occur, therapy is to be interrupted.

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.

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

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population. (see section 4.2).

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 to UV rays should

be avoided unless medically indicated. Patients should use adequate sun-protection to protect themselves from intense sunlight.

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

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

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

Sodium contents
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

NSAIDs including salicylic acid
In animal experiments NSAIDs including salicylic acid caused reduction of tubular methotrexate secretion and consequently increased its toxic effects. However, in clinical studies, where NSAIDs and salicylic acid were given as concomitant medicinal products to patients with rheumatoid arthritis, no increase of adverse reactions was observed. Treatment of rheumatoid arthritis with such medicinal products can be continued during low-dose methotrexate therapy but only under close medical supervision.

Hepatotoxicity
Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the probability of hepatotoxic effects of methotrexate. Alcohol consumption must be avoided during treatment with methotrexate.

Patients taking potentially hepatotoxic and haematoxic medicinal products during methotrexate therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity.

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

Pharmacokinetic interactions
One should be aware of pharmacokinetic interactions between methotrexate, anticonvulsant medicinal products (reduced methotrexate blood levels), and 5-fluorouracil (increased $t_{½}$ of 5--fluorouracil).

Alterations in bioavailability of methotrexate
Salicylates, phenylbutazone, phenytoin, barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability (indirect dose increase). Probenecid and mild organic acids may also reduce tubular methotrexate secretion, and thus cause indirect dose elevations, too.

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

Oral antibiotics such as tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal methotrexate absorption or interfere with the enterohepatic circulation, due to inhibition of the intestinal flora or suppression of bacterial metabolism.

Colestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation. Delayed methotrexate clearance should be considered in combination with other cytostatic medicinal products.

Co-administration of proton-pump inhibitors such as omeprazole or pantoprazole can lead to interactions: concomitant administration of methotrexate and omeprazole has led to a delay in the renal elimination of methotrexate. In combination with pantoprazole, inhibited renal elimination of the 7-hydroxymethotrexate metabolite, with myalgia and shivering, was reported in one case.

Substances that may have adverse effects on the bone marrow
Under (pre-)treatment with substances that may have adverse effects on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Folate metabolism
Co-administration of medicinal products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular caution should therefore also be exercised in the presence of existing folic acid deficiency.
On the other hand, concomitant administration of folinic acid containing drugs or of vitamin preparations, which contain folic acid or derivatives, may impair methotrexate efficacy.

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

Though the combination of methotrexate and sulfasalazine may enhance methotrexate efficacy by sulfasalazine related inhibition of folic acid synthesis, and thus may lead to an increased risk of adverse reactions, these were only observed in single patients within several trials.

Other antirheumatic agents
A rise in the toxicity of methotrexate is generally not anticipated when methotrexate is used concomitantly with other antirheumatic agents (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine).

Cyclosporine
Cyclosporine may potentiate methotrexate efficacy and toxicity. There is an increased risk of renal dysfunction. In addition, there is a biological plausibility of excessive immunosuppression and its associated complications.

Theophylline and caffeine
Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored under concomitant methotrexate administration.
Excessive consumption of beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, 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.

Leflunomide
The combined use of methotrexate and leflunomide may increase the risk for pancytopenia.
Methotrexate leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dose adjustment.

Immune-modulating medicinal products
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.

Vaccines
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).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.
As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to have a teratogenic effect in humans; it has been reported to cause foetal death 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 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.

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

Breastfeeding
As methotrexate is transferred into human milk and may cause toxicity in breast-feeding children, treatment is contraindicated during breast-feeding (see section 4.3). If use of methotrexate during the breast-feeding period should become necessary, breast-feeding is 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.

4.7 Effects on ability to drive and use machines

Nordimet has minor influence on the ability to drive and use machines. Central nervous system (CNS) symptoms, such as fatigue and confusion, can occur during treatment.

4.8 Undesirable effects

Summary of the safety profile
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 most relevant adverse reaction is suppression of the haematopoietic system and gastrointestinal disorders.

List of adverse reactions
Frequencies are defined using the following convention:
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.

Infections and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: lymphoma (see “description” below)

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression, lymphoproliferative

disorders (see “description below”).
Not known: Eosinophilia

Immune system disorders
Rare: Allergic reactions, anaphylactic shock, hypogammaglobulinaemia.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes mellitus.

Psychiatric disorders
Uncommon: Depression, confusion.
Rare: Mood alterations.

Nervous system disorders
Common: Headache, tiredness, drowsiness.
Uncommon: Dizziness.
Very rare: Pain, muscular asthenia, paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: Encephalopathy/ Leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Impaired vision, Retinopathy.

Cardiac disorders
Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders
Rare: Hypotension, thromboembolic events

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, shortness of breath and fever.
Rare: Pulmonary fibrosis, *Pneumocystis jiroveci* pneumonia, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain.
Common: Oral ulcers, diarrhoea.
Uncommon: Gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis.
Rare: Gingivitis.
Very rare: Haematemesis, haematorrhea, toxic megacolon.

Hepatobiliary disorders (see section 4.4)
Very common: Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.
Rare: Acute hepatitis.
Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitivity reactions, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare: Increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.
Not known: Skin exfoliation / dermatitis exfoliative.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.
Rare: Stress fracture.
Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders)

Renal and urinary disorders
Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.
Rare: Renal failure, oliguria, anuria, electrolyte disturbances.
Not known: Proteinuria.

Reproductive system and breast disorders
Uncommon: Inflammation and ulceration of the vagina.
Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

General disorders and administration site conditions
Rare: Fever, wound-healing impairment.
Not known: Asthenia, injection site necrosis, oedema.

Description of selected adverse reactions

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.

The appearance and degree of severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.
Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed with subcutaneous use, decreasing during therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme in UK. Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms of overdose
The adverse toxic effects of methotrexate mainly affect the haematopoietic and gastrointestinal system. Symptoms include leukocytopenia, 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.

Treatment 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 urinary alkalisation may be required to prevent precipitation of methotrexate and/or its metabolites within the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective methotrexate clearance has been reported with acute, intermittent haemodialysis using a high-flux dialyser.
In patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis or psoriasis vulgaris, administration of folic or folinic acid may reduce methotrexate toxicity (gastrointestinal symptoms, inflammation of oral mucosa, hair loss and increase of liver enzymes) (see section 4.5). Prior to using folic acid products, monitoring of vitamin B12 levels is recommended, since folic acid may mask an existing vitamin B12 deficiency, particularly in adults over 50 years of age.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants. ATC code: L04AX03

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

Clinical efficacy and safety
A study of weekly injections of methotrexate in a group of patients with chronically active Crohn's disease (despite at least three months of prednisone therapy), showed that methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone. A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (25 mg weekly) or placebo. After 16 weeks, 37 patients (39.4%) were in clinical remission in the methotrexate group, as compared with 9 patients (19.4%, P=0.025;) in the placebo group. The patients in the methotrexate group received less prednisone overall and their mean score on the Crohn's Disease Activity Index was significantly lower than those in the placebo group (P=0.026 and P=0.002, respectively). [**Feagan** et al (1995)]

A study of patients, who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate, showed that a low dose of methotrexate maintains remission. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg *I.M.* once weekly or placebo for 40 weeks. At week 40, 26 patients (65%) were in remission in the methotrexate group and fewer needed prednisone for relapse (28%), as compared with the placebo group (39%; P=0.04 and 58%, P=0.01, respectively). [**Feagan** et al (2000)]

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

5.2 Pharmacokinetic properties

Absorption
After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m^2 to 80 mg/m^2 BSA), methotrexate has a mean bioavailability of approximately 70%, although considerable inter- and intra-subject variations are possible

(25-100%). Plasma peak concentrations are attained within 1-2 hours. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.

Distribution
Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the body fluids in minimal amounts; under high doses (300 mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the body fluids. Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites).

Biotransformation
Approximately 10% of the administered methotrexate is metabolised intrahepatically. The major metabolite is 7-hydroxymethotrexate.

Elimination
Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced enterohepatic blood flow exists.

In case of renal insufficiency, elimination is delayed significantly. Impaired elimination in presence of hepatic insufficiency is not known.

Methotrexate passes the placental barrier in rats and monkeys.

5.3 Preclinical safety data

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.
Keep the pre-filled pen orpre-filled syringe in the outer carton in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

Pre-filled pen with a 1 mL type I glass syringe with attached stainless steel needle and a chlorobutyl rubber plunger stopper. The pre-filled pens contain 0.3 ml, 0.4 ml, 0.5 ml, 0.6 ml, 0.7 ml, 0.8 ml, 0.9 ml or 1 ml of solution for injection.
Each pack contains 1 pre-filled pen and one alcohol swab and multipacks containing 4 (4 packs of 1 or 1 pack of 4) and 12 (3 packs of 4) pre-filled pens and 4 and 12 alcohol swabs respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with ample amount of water.

Nordimet is for single use only and any unused solution must be discarded.

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

7. MARKETING AUTHORISATION HOLDER

Nordic Group B.V.
Siriusdreef 41
2132 WT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Nordimet 12.5 mg solution for injection in pre-filled pen (PLGB 40621/0025)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2021

10. DATE OF REVISION OF THE TEXT

09/12/2025