EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/527385/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Nordimet

International non-proprietary name: methotrexate

Procedure No.: EMEA/H/C/003983/0000

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List of abbreviations

CEP	Certificate of Suitability of the European Pharmacopoeia
CFU	Colony Forming Units
CRS	Chemical Reference Substance (official standard)
DMARDs	Disease-modifying anti-rheumatic drugs
EDQM	European Directorate for the Quality of Medicines
ERA	Enviromental Risk Assessment
EP	European Pharmacopoeia
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
MTX	Methotrextate
NSAIDs	Nonsteroidal anti- inflammatory drugs
NMT	Not more than
OOS	Out of Specifications
PEC	Predicted Environmental Concentration
Ph. Eur.	European Pharmacopoeia
PUVA	Psoralens and ultraviolet A
RH	Relative Humidity
SmPC	Summary of Product Characteristics
UPLC	Ultra-high performance liquid chromatography

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nordic Group B.V. submitted on 22 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nordimet, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2014. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Nordimet is indicated for the treatment of:

- active rheumatoid arthritis in adult patients,
- polyarthritic forms of severe, active juvenile idiopathic arthritis, 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.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on bibliographic literature.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Lantarel FS Solution for injection 25 mg
  - Marketing authorisation holder: Pfizer Pharma GmbH
  - Date of authorisation: 21- 11- 1991
  - Marketing authorisation granted by:

    Member State (EEA): Germany

    - National procedure
  - Marketing authorisation number: 9709.01.01
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form:

    Lantarel FS Solution for injection 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg.
  - Marketing authorisation holder: Pfizer Pharma GmbH
  - Date of authorisation: 21- 11- 1991
  - Marketing authorisation granted by:

    Member State (EEA): Germany

    - National procedure
  - Marketing authorisation numbers:
    - 9709.01.01
    - 9709.02.01
    - 9709.03.01
    - 9709.04.01
    - 9709.05.01

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Bruno Sepodes

- The application was received by the EMA on 22 June 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 November 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 20 November 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 February 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 April 2016.
- During the PRAC meeting on 14 April 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 18 April 2016.
- During the CHMP meeting on 28 April 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2016.
- During the meeting on 23 June 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nordimet on 23 June 2016.

2. Scientific discussion

2.1. Introduction

Methotrexate is available for clinical use in most countries worldwide and is currently one of the most frequently used disease-modifying anti-rheumatic drugs (DMARDs). The product in this application, Nordimet, is considered a hybrid medicinal product of Lantarel FS 25mg/ml from Pfizer Pharma GmbH, and is available in strengths of 7.5, 10, 15, 20 and 25 mg for intramuscular, intravenous or subcutaneous administration.

No new pre-clinical tests or clinical trials were conducted for this product.

The clinical overview dated August 2015 which was submitted in support of this application was based on published scientific literature.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg or 25 mg of methotrexate as active substance.

Other ingredients are: sodium chloride, sodium hydroxide and water for injections

The product is available in pre-filled pen with a 1 ml type I glass syringe with attached stainless steel needle and a chlorobutyl rubber plunger stopper, as described in section 6.5 of the SmPC. 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.

2.2.2. Active substance

General information

The chemical name of methotrexate is (2S)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid corresponding to the molecular formula $C_{20}H_{22}N_8O_5$ and has a relative molecular mass 454.4 g/mol and the following structure:

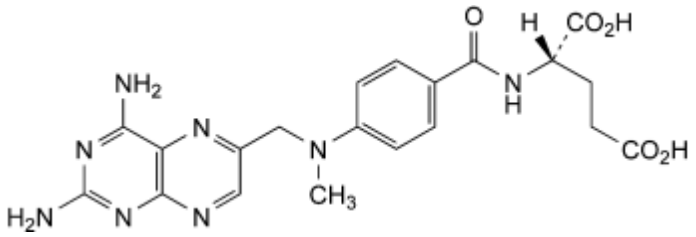

Figure 1. Structural formula of methotrexate.

The active substance is a yellow or orange, crystalline, hygroscopic powder. It is practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates

Methotrexate exhibits stereoisomerism due to the presence of one chiral centre. The active substance corresponds to the (*S*) stereoisomer. Enantiomeric purity is controlled routinely by chiral HPLC.

As there is a monograph of methotrexate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification is in line with the current version of the Ph. Eur. monograph for methotrexate. It includes tests for appearance, identification (IR), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), heavy metals (Ph. Eur.), water (Ph. Eur.), sulfated ash (Ph. Eur.), and is supplemented with a residual solvent test for ethanol (GC) and a test for bacterial endotoxin (Ph. Eur.)

The information concerning the analytical procedures is covered in the CEP. The additional in-house head space gas chromatography method to control the level of ethanol in methotrexate drug substance is also included in the CEP.

Batch analysis data from two commercial scale batches of the active substance analysed by both the active substance and the finished product manufacturer were provided. The results are within the specifications and consistent from batch to batch.

The active substance manufacturer and finished product manufacturer use chemical reference substances from EDQM (EP CRS) for testing the active substance.

Stability

The stability program and results obtained were assessed by EDQM and the re-test period and storage conditions are included the CEP. The re-test period of the active substance is 5 years if stored in double polyethylene bag with outer black bag in fiber drum.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product consists of a clear, yellow 25 mg/ml methotrexate solution for injection with a pH of 8.0-9.0 and an osmolality of approximately 300 mOsm/kg, in pre-fill pen (0.3-1.0 ml filling volume).
1 ml of solution contains 25 mg methotrexate

1 pre-filled pen of 0.3 ml contains 7.5 mg methotrexate.

1 pre-filled pen of 0.4 ml contains 10 mg methotrexate.

1 pre-filled pen of 0.5 ml contains 12.5 mg methotrexate.

1 pre-filled pen of 0.6 ml contains 15 mg methotrexate.

1 pre-filled pen of 0.7 ml contains 17.5 mg methotrexate.

1 pre-filled pen of 0.8 ml contains 20 mg methotrexate.

1 pre-filled pen of 0.9 ml contains 22.5 mg methotrexate.

1 pre-filled pen of 1.0 ml contains 25 mg methotrexate.

The aim of the pharmaceutical development was to develop a methotrexate solution for injection in pre-filled syringes hybrid to the reference product Lantarel FS 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg, with three additional strengths: 12.5 mg, 17.5 mg and 22.5 mg.

Since the manufacturer already had experience with the manufacture of methotrexate 25 mg/ml solution for injection in vials, the development focused on the feasibility to produce finished product in pre-filled syringes. A concentration of 25 mg/ml was used with the aim to fill standard 1 ml syringes to levels of 0.3–1.0 ml. The development work focused on the development and validation of analytical methods, the development and testing of the filling process at pilot scale, the accelerated stability testing, the stopper testing, the production of validation batches and the stability testing of validation batches.

As methotrexate 25 mg/ml solution for injection is a USP and BP compendial product composed of methotrexate active substance dissolved in an isotonic aqueous solution of sodium chloride, adjusted for pH with sodium hydroxide, compatibility studies between the active substance and the excipients were not conducted. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Nonetheless, specific confirmatory studies to define target points for pH for the bulk solution, osmolality and density were conducted. The selection of the target pH for the bulk solution was based on the specification from the USP and BP (being 7.0–9.0), the actual solubility of methotrexate, its stability and the physiologically compatible limits. Based on these, a target pH of 8.2 ± 0.1 was selected. The confirmatory study for osmolality was in line with the expected outcome. Finally, a specific study was undertaken in order to assess the influence of temperature on the density of a 25 mg/ml methotrexate solution, since the final volume adjustment during the manufacturing process was anticipated to be carried out by weight adjustment. The density of the solution was determined against water at three different temperature points.

The main focus of the manufacturing process development was the syringes filling operation. The 0.3 and 1.0 ml filling volumes were selected to conduct these studies since they represent the extremes of the whole range of the fill volumes for the proposed syringes. Process validation data from three batches of each fill volume were presented. All six batches met all acceptance criteria and were found acceptable.

With regards to the choice of the sterilization method, the use of sterile filtration has been justified based on the observed degradation of the product under heat sterilization (121 °C for 15 min), and stability data on the product sterilized by filtration stored under long term, intermediate and accelerated conditions.

In-process controls for microbial contamination and bioburden are used, and conformance with relevant Ph. Eur. monographs has been confirmed.

Packaging materials for the product were selected based on the physicochemical properties of the active substance, the dosage form, stability of the finished product and the marketing requirements. The primary packaging selected is a 1 ml type I glass syringe with attached stainless steel needle and a chlorobutyl rubber plunger stopper. The material complies with Ph. Eur. and EC requirements. The rationale for the selection of the components has been presented. During development two different halobutyl plunger stoppers were tested for the chosen syringe barrel. Based on the results from a stability study on a bulk solution of methotrexate 25 mg/ml filled in syringes with different plunger stoppers, the chlorobutyl rubber plunger stopper was selected for commercial use.

The syringes are placed in a disposable, fixed, single dose unit pen designed to accommodate all registered strengths. To assess the long-term functionality of the pen to deliver the correct volume of the formulation, long term, intermediate and accelerated stability studies conforming to current ICH guidelines were performed. These are described in the stability section of this report. Briefly, samples from 3 batches of 0.3 ml, 0.6 ml and 1.0 ml filling volumes were tested for identity (IR), extractable volume and container closure integrity testing. All samples met the specifications at all time points. Therefore, the choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the finished product consists of four main steps: compounding and pH adjustment, sterilization of the bulk solution by membrane filtration, filling into syringes and packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process is carried out in clean and/or sterile areas reserved for the manufacture of parenteral solutions. The compounding and pH adjustment of the solution are carried out in Class C clean room environment. The sterilization and filling of the syringes are carried out in Class A/B clean room environment.

The bioburden of solution is checked prior to filtration through the first filter. The integrity of both filters is checked after filtration.

The manufacturing process and IPCs correspond to the actual standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the finished product.

Major steps of the manufacturing process have been validated by a number of studies. Data from six pilot scale batches (three with a fill volume of 0.3 ml and three with a fill volume of 1 ml) have been presented. Although some OOS results were observed, these were investigated and it was concluded that they did not affect the process or the intrinsic quality of the product. Based on the data presented and the justification from the OOS it was concluded that the capability of the manufacturing process to produce finished product of intended quality in a reproducible manner was demonstrated.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (methotrexate solution and pen), identification (IR, UPLC), extractable volume, pH, syringe integrity, sub-visible and visible particles, assay (UPLC), related substances (UPLC) uniformity of dosage units (Ph. Eur.),

sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). It also includes autoinjector functionality specifications: extractable volume, injection time, cap removal force and needle extension.

Acceptable justification has been presented to omit colour of solution from the specification. The colour of the methotrexate solution is bright yellow. The colour is very intense and was found to be far outside the range described in Ph. Eur. 2.2.2. No colour change had been observed in any batches throughout the shelf-life. Additionally, during photostability testing the colour of dark and exposed samples showed no non-compliances. The same is applicable for long term stability samples. Therefore it was concluded that the colour was not critical for the quality of the product.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for nine batches three batches of product with 0.3 ml fill volume, three batches of product with 1.0 ml fill volume and three commercial batches with different fill volumes (1.0 ml, 0.6 ml, 0.3 ml) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification have been provided.

Stability of the product

Stability data of six pilot scale batches (three with 0.3 ml fill volume, three with 1.0 ml fill volume) and three commercial scale batches (with fill volumes of 0.3 ml, 0.6 ml or 1.0 ml) of finished product stored under long term conditions at 25 ºC / 60% RH for up to 36 months, under intermediate conditions 30 ºC / 65% RH for up to 12 months, and under accelerated conditions at 40 ºC / 75% RH for up to 6 months according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identification, extractable volume, pH, integrity test, sub-visible particles, visible particles, assay, related substances, uniformity of dosage units, sterility and bacterial endotoxins. The analytical procedures used are stability indicating.

The studies conducted on the pilot scale batches showed satisfactory stability up to 30 months of storage under long term conditions, but some OOS results were observed for all the batches at the 36 month time-point. A borderline OOS result was observed in one of the pilot scale batches at 6 months. This result was attributed to a combination of relatively high content at release and analytical variation. Studies under accelerated conditions showed some OOS results after 6 months of storage. Studies under intermediate conditions showed satisfactory stability after 12 months of storage.

The studies carried out on the commercial scale batches showed satisfactory stability after 24 months of storage under long term conditions. Although one batch showed an OOS for pH at 24 months, this was not observed in the same batch stored under intermediate conditions, and a reanalysis of the sample indicated that the original measurement was an analytical error. Studies under accelerated conditions showed OOS results after 6 months of storage. Studies under intermediate conditions showed satisfactory stability after 12 months of storage.

In addition, one 1.0 ml commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed an increase in an impurity beyond the upper specification limit Moreover, an unknown impurity was also observed at a level close to the specification limit. Therefore, based on these results, it is concluded that the product should be kept protected from light.

In conclusion, based on available stability data, the proposed shelf-life of 2 years stored below 25°C and keeping the pre-filled pen in the outer carton in order to protect from light as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology was submitted, based on up-to-date scientific literature. The overview provided detailed information on the mechanism of action of methotrexate and thus justification that there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The non-clinical aspects of the SmPC are in line with that of the reference product.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant submitted a phase I Enviromental Risk Assessment (ERA) based on prevalence data for each indication. The total PECsurface water was below 0.01 mcg/l and therefore a phase II assessment was not considered necessary in accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.3. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology was submitted which was considered adequate to justify that there is no need for additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with that of the reference product.

The CHMP agreed that no further non-clinical studies are required.

2.4. Clinical aspects

2.4.1. Introduction

Methotrexate is an established drug which has been used safely and effectively in humans for over 50 years in the European Union (EU) and USA. It is currently authorised for long-term use in children and adults by oral and parenteral routes of administration. The recommended starting dose in Lantarel FS, the reference product used in this application, for adult patients with rheumatoid arthritis is 7.5 mg per week which can be up-titrated to 15-20 mg per week. In children (from 3 years) and adolescents with polyarthritic forms of juvenile idiopathic arthritis the recommended dose is 10-15 mg / m2 body surface area / week which in exceptional cases can be increased up to 20-30 mg / m2 body surface area / week. Finally in psoriasis and psoriatic arthritis, the recommended initial dose after a test dose is 7.5 mg per week.

2.4.2. Pharmacokinetics

The clinical pharmacokinetics of methotrexate following oral and systemic administration are well known and no new data on methotrexate disposition were submitted.

Nordimet 25mg/mL solution for injection has been developed as a hybrid generic product with reference to an authorised methotrexate injection product which is available in the following strengths: 7.5mg, 10 mg, 15 mg, 17.5 mg, 20 mg, 25 mg. In addition to these strengths, Nordimet will also be available as 12.5, 17.5 and 22.5 mg, which is acceptable as the additional strengths are within the range of the reference product. The posology recommendations in all indications are in line with those of Lantarel FS.

According to the CHMP Guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), as the test product is an aqueous solution containing the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence can be considered established and no bioequivalence studies are required.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Discussion on clinical aspects

No new pharmacokinetic or pharmacodynamic studies were submitted.

Nordimet is to be administered as an aqueous subcutaneous injection. It has an identical qualitative and quantitative composition in terms of the active substance as its reference medicinal product and also contains the same excipients. Given the accepted bioequivalence between the proposed new product and the marketed reference product, the absence of new data on methotrexate absorption, distribution, metabolism, and excretion in the target population and its potential for drug-drug interactions is acceptable. The additional strengths compared to the reference product are considered acceptable, as they are within the range of strengths of that product and do not impact on the posology recommendations for Nordimet.

2.4.5. Conclusions on clinical aspects

The CHMP considered that the applicant has provided sufficient justification for the lack of clinical studies based on the claim that Nordimet is a hybrid of the reference product Lantarel FS.

As the product contains the same active ingredient in the same concentration and pharmaceutical formulation as the reference product, the lack of bioequivalence studies was considered acceptable.

The literature data and the publicly available information presented in the dossier were considered acceptable and sufficient to support the use of Nordimet in the applied indications.

2.5. Pharmacovigilance

Risk Management Plan

Safety concerns

Important identified risks	Teratogenicity (including foetal death and abortion)
	Increased risk of neoplasia
	Haematological toxicity
	Hepatotoxicity
	Pulmonary toxicity
	Renal toxicity
	Leukoencephalopathy
	Medication error, including overdose from inadvertent daily instead of weekly dosing

Important potential risks	Bone growth defects in the paediatric population
Missing information	Exposure in children younger than 3 years old

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan.

Risk minimisation measures

Important identified risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Teratogenicity (including foetal death and abortion)	Proposed text in SmPC: - Contraindication in section 4.3 Contraindications of the SmPC. - Warnings in sections 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation and 6.6 of the SmPC. Proposed text in PIL: - Risk is mentioned in section 2 What you need to know before you use Nordimet of the PIL. Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable
Increased risk of neoplasia	Proposed text in SmPC: - Warning included in section 4.4 Special warnings and precautions for use of the SmPC. - Risks are listed in section 4.8 Undesirable effects of the SmPC. Proposed text in PIL: - Risk is mentioned in section 4 possible side effects of the PIL. Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable

Important identified risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Haematological toxicity	Proposed text in SmPC: - Contraindication in section 4.3 Contraindications of the SmPC - Warning included in section 4.4 Special warnings and precautions for use of the SmPC - Several interactions are listed in section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC. - Risks are listed in section 4.8 Undesirable effects of the SmPC Proposed text in PIL: - Risk is mentioned in sections 2 What you need to know before you use Nordimet and 4 possible side effects of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable
Hepatotoxicity	Proposed text in SmPC: - Contraindication in section 4.3 Contraindications of the SmPC - Warning included in section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use of the SmPC - Several interactions are listed in section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC. - Risks are listed in section 4.8 Undesirable effects of the SmPC Proposed text in PIL: - Risk is mentioned in sections 2 What you need to know before you use Nordimet and 4 possible side effects of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable

Important identified risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Pulmonary toxicity	Proposed text in SmPC: - Warning included in section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use of the SmPC - Risks are listed in section 4.8 Undesirable effects of the SmPC Proposed text in PIL: - Risk is mentioned in sections 2 What you need to know before you use Nordimet and 4 possible side effects of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable
Renal toxicity	Proposed text in SmPC: - Contraindication in section 4.3 Contraindications of the SmPC - Warning included in section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use of the SmPC - Several interactions are listed in section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC. - Risks are listed in section 4.8 Undesirable effects of the SmPC Proposed text in PIL: - Risk is mentioned in sections 2 What you need to know before you use Nordimet and 4 possible side effects of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable

Important identified risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Leukoencephalopathy	Proposed text in SmPC: - Risk is listed in section 4.8 Undesirable effects of the SmPC Proposed text in PIL: - Risk is mentioned in section 4 Possible side effects of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable
Medication error, including overdose from inadvertent daily instead of weekly dosing	Proposed text in SmPC: - Statement and warning in section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use and 6.4 Special precautions for storage of the SmPC - Risks of overdose are mentioned in section 4.9 Overdose of the SmPC Proposed text in PIL: - Risk is mentioned in section 2 What you need to know before you use Nordimet, 3 How to use Nordimet, and 5 How to store Nordimet of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable

Important potential risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Bone growth defects in the paediatric population	Proposed text in SmPC: - Statement and warning in section 4.2 Posology and method of administration - Risks are listed in section 4.8 Undesirable effects of the SmPC. Proposed text in PIL: - Warning and risks are mentioned in sections 2 What you need to know before you use Nordimet and 4 possible side effects of the PIL. Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable
Missing information		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Exposure in children younger than 3 years old	Proposed text in SmPC: - Statement in section 4.2 Posology and method of administration of the SmPC. Proposed text in PIL: - Risk is mentioned in sections 2 What you need to know before you use Nordimet and 3 How to use Nordimet of the PIL Other routine risk minimisation measures: - Nordimet should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action.	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a hybrid version of methotrexate solution for injection. Additional strengths to those are being proposed but which are within the ranges of strengths of the reference product. The indications of the reference product Lantarel FS are in line with those of Nordimet.

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient, to support the use of Nordimet in its applied indications.

This application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A bioequivalence study was not submitted and this was considered acceptable as Nordimet contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration (parenteral) as the reference product.

The CHMP, having considered the quality data provided as well as the non-clinical and clinical information submitted in the application, is of the opinion that Nordimet is comparable to the reference product Lantarel FS in the applied indications and that no additional risk minimisation activities are required beyond those included in the product information.

Therefore, the benefit risk balance for Nordimet is considered positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nordimet is favourable in the following indications:

- 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.