10 December 2020
EMA/56247/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nordimet

International non-proprietary name: methotrexate

Procedure No. EMEA/H/C/003983/II/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

1. Background information on the procedure 6
1.1. Type II variation 6
1.2. Steps taken for the assessment of the product 6

2. Scientific discussion 7
2.1. Introduction 7
2.1.1. Problem statement 8
2.1.2. About the product 10
2.1.3. The development program 10
2.1.4. General comments on compliance with GCP 10
2.2. Non-clinical aspects 10
2.2.1. Ecotoxicity/environmental risk assessment 10
2.2.2. Conclusion on the non-clinical aspects 10
2.3. Clinical aspects 11
2.3.1. Introduction 11
2.3.2. Pharmacokinetics 11
2.3.3. Pharmacodynamics 14
2.3.4. Discussion on clinical pharmacology 15
2.3.5. Conclusions on clinical pharmacology 15
2.4. Clinical efficacy 16
2.4.1. Dose response study(ies) 16
2.4.2. Main studies 16
2.4.3. Discussion on clinical efficacy 26
2.4.4. Conclusions on the clinical efficacy 29
2.5. Clinical safety 30
2.5.1. Discussion on clinical safety 34
2.5.2. Conclusions on clinical safety 36
2.5.3. PSUR cycle 37
2.6. Risk management plan 37
2.7. Update of the Product information 40
2.7.1. User consultation 40

3. Benefit-Risk Balance 41
3.1. Therapeutic Context 41
3.1.1. Disease or condition 41
3.1.2. Available therapies and unmet medical need 41
3.1.3. Main clinical studies 42
3.2. Favourable effects 42
3.3. Uncertainties and limitations about favourable effects 43
3.4. Unfavourable effects 43
3.5. Uncertainties and limitations about unfavourable effects 44
3.6. Effects Table 44
3.7. Benefit-risk assessment and discussion 44
3.7.1. Importance of favourable and unfavourable effects 44
3.7.2. Balance of benefits and risks 45

3.8. Conclusions 45
4. Recommendations 46
5. EPAR changes 46

List of abbreviations

6-MP	6-Mercaptopurine
7-OH	7-Hydroxy
ACR	American College Of Rheumatology Questionnaire
ADR	Adverse Drug Reaction
AEs	Adverse Events
AICAR	Phosphoribosylamino-Imidazolecarboxoamide
ALAT	Alanine Transaminase
ALT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under The Curve
AZA	Azathioprine
BMI	Body Mass Index
CD	Crohn’s Disease
CDAI	Crohn's Disease Activity Index
CHOP	Children’s Hospital Of Philadelphia
CI	Confidence Interval
CRP	C-Reactive Protein
DAS	Disease Activity Score
DHFR	Dihydrofolate Reductase
DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid.
ECCO	European Crohn's and Colitis Organization
EL	Evidence Level
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
ESR	Erythrocyte Sedimentation Rate
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GST	Gold Sodium Thiomalate
HAQ	Health Assessment Questionnaire
HBI	Harvey Bradshaw Index

HCV	Hepatitis C Virus
IBD	Inflammatory Bowel Disease
IC	Indeterminate Colitis
IFX	Infliximab
IL	Interleukin
IM	Intramuscular
IMM	Immunomodulator
IQR	Interquartile Range
IR	Incidence Rate
IU	International Units
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
MTX	Methotrexate
MTXPG	Polyglutamated Methotrexate Metabolites
NR	Non Response
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PASI	Psoriasis Area Severity Index
PCDAI	Paediatric Crohn's Disease Activity Index
PGA	Physician Global Assessment
PICR	Paediatric IBD Collaborative Research Group Registry
PUVA	Psoralen Ultraviolet A Therapy
RA	Rheumatoid Arthritis
RR	Risk Ratio
SC	Subcutaneous
SD	Standard Deviation
SDS	Standard Deviation Scores
TNF	Tumor Necrosis Factor
TP	Thiopurine
UK	United Kingdom
ULN	Upper Limit of Normal
UVB	Ultraviolet B Therapy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Nordic Group B.V. submitted to the European Medicines Agency on 17 December 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.0 has also been submitted. The MAH took the opportunity to update the RMP with changes related to GVP V version 2 template and the outcome of MTX referral.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: n/a

Timetable	Actual dates
Submission date	17 December 2019
Start of procedure:	1 February 2020
CHMP Rapporteur Assessment Report	17 April 2020
PRAC Rapporteur Assessment Report	23 March 2020
PRAC members comments	6 April 2020
Updated PRAC Rapporteur Assessment Report	8 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 April 2020
Request for supplementary information (RSI)	30 April 2020
CHMP Rapporteur Assessment Report	18 August 2020
PRAC Rapporteur Assessment Report	26 August 2020
PRAC members comments	20 August 2020
PRAC Outcome	4 September 2020
CHMP members comments	7 September 2020
Updated CHMP Rapporteur Assessment Report	13 September 2020
2nd Request for supplementary information	17 September 2020
CHMP Rapporteur Assessment Report	15 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC members comments	18 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur Assessment Report	05 December 2020
Opinion	10 December 2020

2. Scientific discussion

2.1. Introduction

Methotrexate is an established drug which has been used 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. It is indicated in the treatment of cancers such as acute lymphoblastic leukaemia (ALL) and various inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, and psoriatic arthritis and as steroid sparing adjunctive therapy in Crohn's disease. Each group of indications has a different administration schedule:

- For the treatment of cancer, various administration schedules including daily dosage may be used;

- For the treatment of autoimmune diseases, which require immunosuppressive therapy like rheumatoid arthritis, psoriasis, Crohn's disease and other autoimmune diseases, it is prescribed as a single low-dose, once a week.

The product in this application, Nordimet, was authorised 18/08/2016 as a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC referring to the reference product Lantarel FS 25mg/ml from Pfizer Pharma GmbH. Nordimet is supplied in prefilled pens for subcutaneous use containing volumes ranging from 0.3 to 1ml. One ml of solution contains 25 mg of methotrexate.

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.

The Marketing authorisation holder applies in this extension of Indication application for the indication "treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines".

The reference product does not include the proposed therapeutic indication.

2.1.1. Problem statement

Disease or condition

Crohn's disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. Some patients may have a continuously clinically active disease.

Claimed the therapeutic indication

The MAH applied for an indication in the "Treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines"

The proposed dosing regimen were as follows:

Dosage in adult patients with Crohn's disease:

- Induction treatment: 25 mg/week administered subcutaneously.

Response to treatment can be expected after approximately 8 to 12 weeks.

- Maintenance treatment: 15 mg/week administered subcutaneously.

Dosage in children and adolescents with Crohn's disease:

- Induction treatment: 15 mg/m2 BSA/week to a maximum of 25 mg administered subcutaneously.

Response to treatment can be expected after approximately 8 to 12 weeks.

- Maintenance treatment: Children: 10 mg/ m2 BSA/week to a maximum of 15 mg administered subcutaneously.

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

Epidemiology

Crohn Disease disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (approximately 40%), followed by a disease in the small bowel only (approximately 30%), in the colon only (approximately 25%), and other locations (approximately 5%). It occurs in all ages with a higher incidence in the younger population and there is no marked sex difference. The incidence of CD in European countries is estimated to be 6-8.5/100.000. Recent epidemiological studies have found increased mortality risk in patients with severe CD and most individuals experience an impact of the disease on their daily life.

Aetiology and pathogenesis

In the absence of specific markers or aetiological mechanisms, a diagnosis is usually based on composite clinical and pathological features and the exclusion of alternative disease states. CD has been classified by disease phenotype into primarily inflammatory disease, stricturing disease or penetrating disease modified by the presence of upper gastrointestinal or perianal disease (Montreal classification 2005). Over the course of the disease, phenotype commonly changes from predominantly inflammatory disease to stricturing and/or penetrating disease.

Clinical presentation

The symptoms are partly determined by the anatomical location and the severity of the disease and there may be no direct correlation between an individual's symptoms and endoscopic and radiological findings. The major signs and symptoms are diarrhoea, abdominal pain and weight loss. Physical findings reflect the site and severity of the pathology. Abdominal tenderness or presence of an abdominal mass reflects serosal inflammation or abscess formation. Perianal manifestations are common (up to 20% of patients). Extraintestinal manifestations include ocular inflammation, arthropathies, skin lesions and a spectrum of hepatic diseases. Due to their transmural nature, inflammatory lesions can result in the formation of strictures, fistulae and penetration, which can lead to obstruction and abscesses, respectively.

Management

Remission can be achieved either by medical treatment or surgery. Medical therapy recommended by clinical guidelines includes corticosteroids, immunosuppressant drugs and biologics (anti-tumour necrosis factor (TNF) α agents and adhesion molecule inhibitors). Nutritional support also has a role as primary therapy (in children) or as adjunct to other treatment. When medical treatment is unsuccessful or with certain complications, surgery is indicated. More than 70% of patients with ileal disease will require surgery at least once during the course of their disease.

2.1.2. About the product

The antimetabolite, anticancer drug methotrexate (MTX) has been shown to be efficacious at a low dosage (25 mg or less once a week) for several chronic inflammatory diseases, including rheumatoid arthritis (RA) and psoriasis. These observations led to the empiric use of low-dose MTX as a treatment for refractory IBD [Kozarek et al (1989) in Egan et al (1996)]. MTX inhibits dihydrofolate reductase, resulting in impaired DNA synthesis. Additional anti- inflammatory properties may be related to decreased IL-1 production. Intramuscular or subcutaneous MTX (25 mg/week) is effective in inducing remission and reducing glucocorticoid dosage; 15 mg/week is effective in maintaining remission in active CD [Friedman and Blumberg (2015)].

Optimal treatment for CD involves controlling the immune response and reducing the inflammatory cascade. Immune-modifier and anti- inflammatory effects of low-dose MTX that could potentially be therapeutic for patients with Crohn's disease therefore include antiproliferative effects on leukocytes; decreased immunoglobulin production; decreased eicosanoid production, especially leukotriene B4 [Eliakim et al (1992) in Egan et al (1996)]; decreased production of pro- inflammatory cytokines; and local release of adenosine at sites of inflammation. The beneficial effect of MTX therapy for IBD is likely mediated by a combination of these, and possibly other actions [Egan et al (1996)].

2.1.3. The development program

No new pre-clinical tests or clinical trials were conducted in support of this variation. The MAH submitted a new Clinical Overview with more recent literature data for methotrexate use in CD in adult and paediatric patients. These studies are retrospective, clinically based studies, including paediatric data. The MAH did not seek Scientific advice at the CHMP.

2.1.4. General comments on compliance with GCP

Not applicable the application is based on literature data.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant determined the PEC value for this indication and recalculated the total PEC surface water based on the sum of the single PEC for each indication described in the updated SmPC. The total PEC surface water is below 0.01 µg/L and Phase II assessment is not considered necessary. Therefore, this medicinal product is unlikely to represent a risk for the environment.

2.2.2. Conclusion on the non-clinical aspects

The total PEC surface water is below 0.01 µg/L and Phase II assessment is not considered necessary. This medicinal product is unlikely to represent a risk for the environment.

2.3. Clinical aspects

2.3.1. Introduction

Searches were carried out in bibliographic (EMBASE from 1995, MEDLINE/TOXLINE from 1966) databases. Specific search criteria were used, adjusted to the specific database terminology, scope and structure, covering all aspects required for this overview. Primarily English language peer-reviewed literature was selected initially on the basis of search results including abstracts, and subsequently on the basis of original publications acquired. Where necessary, reference lists of original publications were searched manually for complementary publications. Moreover, recent issues of authoritative textbooks were used as well as Professional Drug Reference sources.

GCP

Not applicable, the application is based on published literature.

2.3.2. Pharmacokinetics

Absorption

Methotrexate 25 mg/ml solution for injection in pre-filled syringe is administered intramuscularly, intravenously or subcutaneously. Since the test product Methotrexate 25 mg/ml solution for injection is to be administered as an aqueous parenteral (subcutaneous, intravenous or intramuscular) solution containing the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved no bioequivalence studies are required.

The following characteristics of the product under consideration are compared with the characteristics of the products used in the literature references and with approved products:

Administration route

Available evidence and recommendations from the second European evidence-based consensus on the diagnosis and management of Crohn's disease indicate that intramuscular or subcutaneous methotrexate administration in a dosage of 25 mg/day may be used in adult patients with active Crohn's disease (CD) who do not respond to or who do not tolerate thiopurine or anti-tumour necrosis factor (TNF) treatment.

Consensus guidelines from ECCO/ESPGHAN on the medical management of paediatric Crohn's disease state that methotrexate is usually administered via SC injection. SC injection is likely as effective as IM injection and associated with increased adherence. The bioavailability of oral methotrexate is highly variable and there are no comparative studies with the parenteral route.

The currently valid ECCO Guideline/Consensus paper published in November 2016, states that the prospective controlled trials that demonstrated efficacy in CD used an intramuscular or subcutaneous route. A significant reduction of drug levels and variability in the absorption of oral methotrexate as compared to subcutaneous administration has been demonstrated, which may explain why parenteral administration seems to be more effective. However, for practical reasons relating to the reconstitution of parenteral cytotoxic drugs, oral dosing is more convenient and often preferred by patients. Consequently, treatment should usually be started via the intramuscular or subcutaneous routes. A

switch to oral administration may be attempted for maintenance while carefully monitoring the clinical response, although no trials are available to support this approach.

The product under consideration, Methotrexate 25 mg/ml solution for injection, is administered via SC injection. Therefore, Methotrexate 25 mg/ml solution for injection has the same administration route as what is recommended in current evidence-based European consensus guidelines.

Type of solution, concentration, dosage and qualitative composition

The Bioequivalence (BE) guideline states the following for parenteral solutions:

"In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity."

Table 1 A summary table of the type of solution, dosage and concentration of the products used in the studies demonstrating the efficacy of MTX in Crohn's disease

Reference	Method of admini-stration	Dosage	Concentration	Type of solution	Product	MAH
Ardizzone et al (2003)	IV	25 mg/week				
Feagan et al (1995)	IM	25 mg/week	25 mg/ml	Aqueous	Rheumatrex*	Lederle (= Wyeth = Pfizer)
Feagan et al (2000)	IM	15 mg/week	25 mg/ml	Aqueous	Rheumatrex*	Wyeth (= Pfizer)
Feagan et al (2014)	SC	10-25 mg/week	25 mg/ml	Aqueous	Mayne Pharma, Novopharm, Bedford	
Mahadevan et al (2003)	IM	25 mg/week				
Wahed et al (2009)	IM and oral	15-25 mg/week				

IV, intravenous; IM, intramuscular; SC, subcutaneous; MAH, marketing authorisation holder
* The exact composition of Rheumatrex could not be retrieved. Therefore, the composition of Methotrexate Injection, USP from Pfizer was used as both products belong to the same global marketing authorisation.

As shown in the table above, a number of studies that demonstrated the efficacy of methotrexate in Crohn's disease used an intramuscular or subcutaneous delivery route. In particular, the studies conducted by Feagan et al (1995 and 2000) used an aqueous solution administered by IM injection and the study by Feagan et al (2014) also used an aqueous, which was subcutaneously injected. (For the other studies in which methotrexate was administered parenterally, it was not possible to determine the type of solution used.)

As indicated in the table above, the products used in the pivotal studies by Feagan et al (1995, 2000), belong to the same global marketing authorization from Pfizer. As the reference product for the product under consideration (Lantarel FS 25 mg) also belongs to Pfizer, the products used in the pivotal studies by Feagan et al (1995, 2000) belong to the same global marketing authorization as to which this application refers to.

The product under consideration, Methotrexate 25 mg/ml solution for injection, is also an aqueous solution for injection to be administered SC.

Concentration

The concentration of the products used in the pivotal studies by Feagan et al (1995, 2000) was not included in the references. Also, for the pivotal study by Feagan et al (2014), the concentration of the

products used was not included. However, the names of the products used are mentioned as MaynePharma, Bedford laboratories and Novopharm.

The concentrations of these products are:

- Bedford Laboratories: 25 mg/ml
- Maynepharma: 25 mg/ml
- Novopharm: 25 mg/ml

Therefore, it can be assumed that the concentration of the products used in the pivotal studies is the same as the concentration of the product under consideration.

Composition

Based on the table below, the applicant concludes that the qualitative composition of the product under consideration is comparable to the reference product Lantarel and also to the products used in the pivotal studies by Feagan et al (1995, 2000, 2014).

Table 2 The composition of the products used in the pivotal studies by Feagan and al (1995, 2000, 2014), as stated in the product information compared with the composition of methotrexate 25mg/ml solution for injection and the reference product Lantarel FS 25mg

Composition	Bedford	Mayne Pharma	Novopharm	Rheumatrex*	Lantarel FS	Methotrexate solution for injection
Methotrexate	X	X	X	X	X	X
Sodium chloride	X	X	X	X	X	X
Water for injection	X	X	X	X	X	X
Sodium hydrochloride	X	X	X	X	X	X
Hydrochloric acid	X if needed	X if needed	X	X		
Benzyl alcohol		X				

*The exact composition of Rheumatrex is not known anymore. Therefore, the composition of Methotrexate Injection, USP from Pfizer was used as both products belong to the same global marketing authorisation.

The quantitative composition is not known for the products used in the pivotal studies by Feagan et al (1995, 2000, 2014). However, the function of the excipients used is to either dissolve the methotrexate or to prepare an isotonic solution. Therefore, as long as the solution is isotonic and the methotrexate is dissolved completely, the applicant is of the opinion that any deviations in the quantitative composition of the excipients will not affect the efficacy and safety of the product.

The Applicant considered that there is sufficient evidence available that support a bridge between clinical data from literature to a methotrexate solution for injection with a concentration between 10 mg/ml and 50 mg/ml. As the product under consideration has a 25 mg/ml concentration, the bridge between clinical data available in the literature and the product under consideration is established.

The pharmacokinetics of subcutaneous methotrexate were comparable with those of intramuscular methotrexate, the former mode of administration being more convenient and less painful. The drug is absorbed more rapidly and reaches higher serum concentrations after intramuscular or subcutaneous administration compared with the oral route. The bioavailability of methotrexate is 11% to 15% lower after oral administration than those of the intramuscular or subcutaneous administration; but on the other hand, no differences between intramuscular and subcutaneous dosing exist. Nevertheless, the mean absolute bioavailability is very similar, suggesting that the routes of low dose pulse methotrexate administration are interchangeable. Factors such as sex, age, body weight, creatinine clearance, dose, and concomitant medications may also contribute to methotrexate variability.

Distribution

No new data was presented. This was considered acceptable by the CHMP.

Elimination

No new data was presented. This was considered acceptable by the CHMP.

Dose proportionality and time dependencies

No new data was presented. This was considered acceptable by the CHMP.

Special populations

No new data was presented. This was considered acceptable by the CHMP.

Pharmacokinetic interaction studies

No new data was presented. This was considered acceptable by the CHMP.

Pharmacokinetics using human biomaterials

No new data was presented. This was considered acceptable by the CHMP.

2.3.3. Pharmacodynamics

Mechanism of action

Methotrexate is an antimetabolite that exerts its action by competing with folic acid for the enzyme dihydrofolate reductase. By inhibiting dihydrofolate reductase methotrexate interferes with DNA synthesis by reducing purine and pyrimidine supply in rapidly dividing cells.

Methotrexate has shown that is causes a dose-dependent suppression of T-cell activation and adhesion molecule expression. The suppression of intercellular adhesion molecule-l was adenosine and folate dependent, while methotrexate suppression of the skin-homing cutaneous lymphocyte-associated antigen was adenosine independent [Johnston et al (2005) in Niehues et al (2006)].

When administered at the high doses used for cancer chemotherapy, MTX has both anti-proliferative and immunomodulating activity [Jolivet et al (1983a), Otterness et al (1976) in Egan et al (1996)]. Researchers have sought to identify the cellular and physiologic effects of low-dose MTX therapy, which underlie its efficacy in chronic inflammatory diseases [Cronstein et al (1992) in Egan et al (1996)]. In particular, whether low-dose MTX therapy has pronounced anti-proliferative activity is unclear; however, if it does, the efficacy of MTX for chronic inflammation could be due to immunomodulation mediated by inhibition of leukocyte proliferation and function. Alternatively, MTX efficacy could relate to some anti-inflammatory action independent of its inhibition of DNA, RNA, and protein synthesis. The physiologic effects of MTX reported to date are summarized in the table below.

Table 3 Physiological effects of the biochemical actions of MTX

Action	Physiologic effect
Inhibition of thymidylate and purine synthesis, impairing DNA, RNA, and protein synthesis	Possible reduction of leukocyte proliferation
Decrease in production of cytokines and eicosanoids	Decrease in proinflammatory cellular signaling
Depletion of methionine	Decrease in transmethylation-dependent reactions, including immunoglobulin production
Accumulation of adenosine	Lymphotoxic Decrease in immunoglobulin production, leukocyte-endothelial cell adhesion, and leukocyte accumulation and function at sites of inflammation

Primary and secondary pharmacology

No secondary pharmacodynamic studies have been performed. This was considered acceptable by the CHMP.

2.3.4. Discussion on clinical pharmacology

In this application, no new studies were presented and the rationale is based on published clinical studies. The limited information on the MTX pharmacokinetics in patients with Crohn's disease is in line with what has been already described in the other disease populations.

The applicant performed an extensive search on the literature on the use of MTX for Crohn's disease, administered by SC injection. The applicant also identified the products used in the literature studies and the concentrations used. Similar concentration and similarity in qualitative composition was observed between the formulations used. Although quantitative composition of the formulations used in the published studies is not known, their function is simply to prepare an isotonic solution and, as such, all formulations are expected to perform similarly. Overall, the conclusions observed in the published clinical studies can be extrapolated to the current formulation for Nordimet.

Immune-modifier and anti-inflammatory effects of low-dose MTX that could have an therapeutic impact on patients with Crohn's disease include antiproliferative effects on leukocytes, decreased immunoglobulin production, decreased eicosanoid production, especially leukotriene B4 [Eliakim et al (1992) in Egan et al (1996)], decreased production of proinflammatory cytokines and local release of adenosine at sites of inflammation. The beneficial effect of MTX therapy for IBD is likely mediated by a combination of these, and possibly other actions.

2.3.5. Conclusions on clinical pharmacology

In the published studies submitted with this application, aqueous solutions were administered by SC route, with same concentrations and very similar qualitative compositions to the Nordimet formulation. From the biopharmaceutical perspective, the CHMP concluded that the conclusions observed in those studies can be extrapolated to Nordimet.

The beneficial effect of MTX therapy for Crohn Disease is likely mediated by a combination of immune-modifier and anti-inflammatory effects.

2.4. Clinical efficacy

Clinical efficacy of methotrexate in Crohn´s disease is based on literature review.

- RCT (Feagan et al, 1995; Feagan et al, 2000)
- Open label studies
- Retrospective studies
- Cochrane reviews (Mcdonald, 2014 and Patel,2014)
- Clinical guidelines from ECCO, AGA

2.4.1. Dose response study(ies)

No dose response studies were submitted. This was considered acceptable by the CHMP.

2.4.2. Main studies

RCT studies for methotrexate efficacy in CD were presented for induction of response/or remission and for maintenance therapy.

Feagan et al (1995)

Feagan et al (1995) conducted a double-blind, placebo-controlled multicentre study of weekly injections of methotrexate in patients who had chronically active CD despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. The primary outcome measure was clinical remission at the end of the 16-week trial. Remission was defined by the discontinuation of prednisone and a score of <150 points on the Crohn's Disease Activity Index (CDAI). A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (94 patients) or placebo (47 patients). After 16 weeks, 37 patients (39.4%) were in clinical remission in the methotrexate group, as compared with 9 patients (19.1%) in the placebo group (p = 0.025; RR, 1.95; 95% CI, 1.09 to 3.48). The patients in the methotrexate group received less prednisone overall than those in the placebo group (p = 0.026). The mean (±SE) score on the CDAI after 16 weeks of treatment was significantly lower in the methotrexate group (162±12) than in the placebo group (204±17, p = 0.002). The changes in quality-of-life scores and serum orosomucoid concentrations were similar. In the methotrexate group, 16 patients (17 %) withdrew from treatment because of adverse events (including asymptomatic elevation of serum aminotransferase in 7 and nausea in 6), as compared with 1 patient (2 %) in the placebo group. The conclusion of Feagan et al (1995) was that in a group of patients with chronically active CD, methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4 ***Summary of Efficacy for trial Feagan, 1995, NEJM***

Title: Methotrexate for the treatment of Crohn´s disease				
Study identifier	Feagan, 1995, NEJM			
Design	Multicenter double blind placebo controlled; 2:1 ratio			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks not applicable not applicable	
Hypothesis	Methotrexate superior to placebo in steroid dependent patients			
Treatments groups	25mg/ IM injection		25 mg of methotrexate/ week IM (Rheumatrex, Lederle Laboratories, Pearl River, N.Y.) 94 patients (59* and 35**)	
	Placebo		Placebo IM weekly injection 47 patients (30* and 17*)	
Endpoints and definitions	Primary endpoint	Remission	Definition Discontinuation of prednisolone dose and CDAI score <150	
	Secondary endpoint	Prednisolone dose	Decrease in prednisolone dose	
	Secondary Endpoint	Disease activity	CDAI score Inflammatory Bowel Disease Questionnaire (IBDQ) mean serum orosomucoid concentration	
Database lock	Unknown			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Methotrexate IM	Placebo	
	Number of subject	94	47	
	Remission	37 (39%)	9(19%)	p=0.025
		1.95 (1.09 to 3.38) *39% **40%	*10% **35%	
	CDAI score	170 (±7)	193 (±17)	P=0.003
	IBDQ mean serum orosomucoid concentration	169±4 82±3mg/dL	151±6 97±6 mg/dL	P<0.00 P=0.003

Notes	Ppulation included: chronically active disease with at least three months of symptoms despite daily doses of at least 12.5 mg of prednisone with at least one attempt to discontinue treat- ment. Patients who had received long-term prednisone therapy at low doses (☐10 mg per day) were ineligible, as were critically ill patients *high group strata- patients with prednisolone dose > 20mg previously to ransomization **Low group strata prednisolone (was increased to 20mg at randomization)			

Table 5 ***Summary of Efficacy for trial*** **Feagan-2000**

Title: A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease			
Study identifier	Feagan-2000		
Design	A double-blind, placebo-controlled, multicenter study of patients with chronically active Crohn's disease who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for Crohn's disease were permitted. The efficacy of treatment was compared by analyzing the proportion of patients who remained in remission at week 40. Remission was defined as a score of 150 or less on the Crohn's Disease Activity Index.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 – 24 weeks (previous study) 40 weeks not applicable
Hypothesis	Superiority		
Treatments groups	MTX		Methotrexate 15 mg, intramuscularly, once weekly for 40 weeks, 40 patients randomized
	Placebo		Placebo intramuscularly once weekly for 40 weeks, 40 patients randomized
Endpoints and definitions	Primary endpoint	Relapse	Occurrence of a relapse of Crohn's disease, defined as an increase in the Crohn's Disease Activity Index score of at least 100 points above the base-line value or the initiation of prednisone, an antimetabolite, or the two in combination for the treatment of symptoms of Crohn's disease.
	Secondary	NfP	Need for prednisone.
	Secondary	TMAR	Treatment with Methotrexate after Relapse. Among the patients who relapsed, the proportion who re-entered remission after treatment with methotrexate at a higher dose (25 mg once weekly) was assessed
	Safety endpoint	Safety	Occurrence of adverse drug reactions (causal relation and severity)
Database lock	Unkown (publication does not specify)		

Results and Analysis

Primary endpoint:
Fewer patients in the methotrexate group than in the placebo group discontinued treatment before the 40-week study ended (17 of 40 [42%] vs. 23 of 36 [64%], P=0.06). After 40 weeks, the proportion of patients who remained in remission was higher in the methotrexate group than in the placebo group (26 of 40 [65%] vs. 14 of 36 [39%]; unadjusted P=0.04; P=0.01 after adjustment for the route of entry into the trial and study center; absolute reduction in the risk of relapse, 26.1 percent; 95 percent confidence interval, 4.4% to 47.8%). Seventy-eight percent of the relapses met both criteria for relapse; 22 percent met only the criterion of the need for treatment of active disease. None of the potential prognostic variables evaluated were significantly associated with relapse. The median duration of remission was estimated to be 22 weeks in the placebo group. Fewer than 50 percent of the patients in the methotrexate group had relapsed by the end of the study. Therefore, the median duration of remission in this group could not be determined, but it was longer than 40 weeks. In the Cox regression model, treatment with methotrexate was significantly associated with the duration of remission with or without adjustment for the effects of study center and route of entry into the study (adjusted and unadjusted P=0.04).

Use of Prednisone for Relapses
Patients in the methotrexate group had fewer relapses than those in the placebo group and thus were less likely to receive prednisone. Eleven patients (28%) in the methotrexate group received prednisone, as compared with 21 patients (58%) in the placebo group (P=0.01). Among the patients who received prednisone, the total dose of prednisone and the average duration of use were similar in the two groups: 2242 g and 126 days in the methotrexate group and 2071 g and 122 days in the placebo group.

Treatment with Methotrexate after Relapse
Of the 36 patients who relapsed (14 in the methotrexate group and 22 in the placebo group), 22 patients (61 percent) were subsequently given 25 mg of methotrexate once weekly, usually in addition to prednisone. Twelve of these 22 patients (55 percent) successfully discontinued prednisone and were in remission at week 40. Conversely, of the 14 patients who did not receive methotrexate after relapse, only 2 patients (14 percent) were in remission at week 40.

Adverse Events
None of the patients in the methotrexate group had a severe adverse event, as compared with two in the placebo group (one had cervical dysplasia, and the other had a viral respiratory tract infection). One patient who received methotrexate withdrew from the trial prematurely because of nausea. Although nausea and vomiting occurred more frequently among patients in the methotrexate group, none of the symptoms were severe, and only one patient discontinued treatment because of these symptoms. No patient had leukopenia that was severe enough to require withholding treatment or withdrawal from the study. The overall incidence of adverse events was similar in the two groups.

Analysis description	**Primary Analysis**		
Analysis population and time point description			
Descriptive statistics and estimate variability	Treatment group	MTX *{as per above terminology}*	Placebo *{as per above terminology}*
	Number of subjects	40	36
	Relapse (N [%])	14 [35%]	22 [61%]
	NfP (N [%])	11 [28%]	21 [58%]
Effect estimate per comparison	Primary endpoint, Relapse	Comparison groups	MTX and Placebo
		Comparison of proportions	point estimate not reported
		variability statistic	variability not applicable

		P-value (Cox regression model)	P=0.01
	Secondary endpoint, NfP	Comparison groups	MTX and Placebo
		Comparison of proportions	point estimate not reported
		variability statistic	variability not applicable
		P-value (Cox regression model)	P=0.01
Notes	The authors found methotrexate to be an effective and safe maintenance therapy for patients with Crohn's disease. Before enrolling in this study, the patients had entered clinical remission and had stopped taking prednisone after 16 to 24 weeks of therapy with methotrexate. Over the next 10 months significantly more patients in the methotrexate group than in the placebo group remained in remission. Moreover, 72 percent of the patients in the methotrexate group did not require prednisone treatment for recurrent symptoms, as compared with 42 percent of those in the placebo group. In addition, re-treatment with a higher dose of methotrexate (25 mg), usually in combination with prednisone, induced remission in over half the patients who had relapsed. Although these data are observational and thus should be interpreted with caution, these findings suggest that many patients who relapse while receiving low-dose maintenance therapy with methotrexate might ultimately be able to discontinue prednisone therapy if the dose of methotrexate is increased. Because of the long-term consequences of prolonged corticosteroid therapy, maintenance therapy with methotrexate may be preferable The authors estimated that 80 percent of the patients in the placebo group would have a relapse. Randomization of 110 patients would give the study a power of 80 percent to detect a clinically important absolute difference of 25 percent in the primary outcome between the study groups. However, the rate of recruitment was slower than expected, since many patients who had been successfully treated with open-label methotrexate were unwilling to participate in a placebo-controlled trial. For administrative reasons (primarily the impending unavailability of the study drugs because the authors were unable to locate a manufacturer that could continue to supply methotrexate and placebo according to the necessary specifications), enrollment was stopped after 76 patients had undergone randomization. This number of patients gave the study a power of 68 percent to detect an absolute difference of 25 percent between the treatment groups.		

Analysis performed across trials (pooled analyses and meta-analysis)

The Cochrane collaboration

Mcdonald et al (2014)

Systematic review to evaluate the efficacy and safety of methotrexate for induction of remission in patients with active Crohn's disease in the presence or absence of concomitant steroid therapy. They selected randomised controlled trials of methotrexate compared to placebo or an active comparator for treatment of active refractory CD in adult patients (> 17 years). The primary outcome was failure to enter remission and withdraw from steroids. Secondary outcomes included adverse events, withdrawal due to adverse events, serious adverse events and quality of life. Seven studies (495 patients) were included in the review [Ardizzone et al (2003), Arora et al (1999), Feagan et al (1995), Feagan et al (2014), Maté-Jiménez et al (2000), Oren et al (1997), and Schröder et al (2006) in Mcdonald et al (2014)]. Four studies were rated as low risk of bias. Three studies were rated as high risk of bias due to open label or single-blind designs. The seven studies differed with respect to participants, intervention, and outcomes to the extent that meta-analysis was considered to be inappropriate.

GRADE analyses indicated that the quality of evidence was very low to low for most outcomes due to sparse data and inadequate blinding.

Conclusions:

"Based on presented above data, there seems to be an evidence from a single large randomised trial by Feagan et al (1995), that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory CD. Lower dose oral methotrexate does not appear to provide any significant benefit relative to placebo or active comparator. However, these trials were small and further studies of oral methotrexate might be justified. Comparative studies of methotrexate to drugs such as azathioprine or 6- mercaptopurine would require the randomisation of large numbers of patients. The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infliximab monotherapy, although it leads to statistically significant lower anti-IFX antibody levels potentially resulting in fewer instances of infusion reactions or secondary non-response to IFX beyond 50 weeks. These studies were relatively small and further research would be needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies [Mcdonald et al (2014), Feagan et al (1995)]."

Methotrexate for maintenance of remission in Crohn's disease

Once remission in CD is induced, patients often require long-term maintenance therapy in order to prevent relapse and avoid chronic corticosteroid use. This generally requires the use of immunosuppressive agents (as steroid sparing agents).

The Cochrane collaboration

Patel et al (2014) performed a systematic review to evaluate the efficacy and safety of methotrexate for maintenance of remission in patients with CD. Randomised controlled trials that compared methotrexate to placebo or any other active intervention for maintenance of remission in CD were eligible for inclusion. The primary outcome measure was the proportion of patients maintaining clinical remission as defined by the studies and expressed as a percentage of the total number of patients randomized (intention-to-treat analysis). Five studies (n = 333 patients) were included in the review **[Feagan et al (2000), Feagan et al (2014), Maté-Jiménez et al (2000), Oren et al (1997), and Schröder et al (2006) in Patel et al (2014)].** Three studies were judged to be at low risk of bias. Two studies were judged to be at high risk of bias due to blinding. Intramuscular methotrexate was superior to placebo for maintenance of remission at 40 weeks follow-up. Sixty-five per cent of patients in the intramuscular methotrexate group maintained remission compared to 39% of placebo patients (RR 1.67, 95% CI 1.05 to 2.67; 76 patients). The number needed to treat to prevent one relapse was four. A GRADE analysis indicated that the overall quality of evidence supporting this outcome was moderate due to sparse data (40 events). There was no statistically significant difference in maintenance of remission at 36 weeks follow-up between oral methotrexate (12.5 mg/week) and placebo. Ninety per cent of patients in the oral methotrexate group-maintained remission compared to 67% of placebo patients (RR 1.67, 95% CI 1.05 to 2.67; 22 patients). A GRADE analysis indicated that the overall quality of evidence supporting this outcome was low due to very sparse data (17 events). A pooled analysis of two small studies (n = 50) showed no statistically significant difference in continued remission between oral methotrexate (12.5 mg to 15 mg/week) and 6-mercaptopurine (1 mg/kg/day) for maintenance of remission. Seventy-seven per cent of methotrexate patients-maintained remission compared to 57% of 6-mercaptopurine patients (RR 1.36, 95% CI 0.92 to 2.00). A GRADE analysis indicated that the overall quality of evidence supporting this outcome was very low due to high risk of bias in one study (no blinding) and very sparse data (33 events). One small (13 patients) poor quality study found no difference in continued remission between methotrexate and 5-aminosalicylic acid (RR

2.62, 95% CI 0.23 to 29.79). A pooled analysis of two studies (n = 145) including one high quality trial (n = 126) found no statistically significant difference in maintenance of remission at 36 to 48 weeks between combination therapy (methotrexate and infliximab) and infliximab monotherapy. Fifty-four percent of patients in the combination therapy group-maintained remission compared to 53% of monotherapy patients (RR 1.02, 95% CI 0.76 to 1.38, P = 0.95). A GRADE analysis indicated that the overall quality of evidence supporting this outcome was low due to high risk of bias in one study (no blinding) and sparse data (78 events). Adverse events were generally mild in nature and resolved upon discontinuation or with folic acid supplementation. Common adverse events included nausea and vomiting, symptoms of a cold, abdominal pain, headache, joint pain or arthralgia, and fatigue.

Patel et al (2014) conclude that moderate quality evidence indicates that intramuscular methotrexate at a dose of 15 mg/week is superior to placebo for maintenance of remission in CD. Intramuscular methotrexate appears to be safe. Low dose oral methotrexate (12.5 to 15mg/week) does not appear to be effective for maintenance of remission in Crohn's disease. Combination therapy (methotrexate and infliximab) does not appear to be any more effective for maintenance of remission than infliximab monotherapy. The results for efficacy outcomes between methotrexate and 6-mercaptopurine and methotrexate and 5-aminosalicylic acid were uncertain. Large-scale studies of methotrexate given orally at higher doses for maintenance of remission in CD may provide stronger evidence for the use of methotrexate in this manner. These findings are consistent across all the studies.

Clinical studies in special populations

Children

In the clinical review article on the use of MTX in the treatment of inflammatory bowel diseases by Herfarth et al (2016) it is acknowledged that there are no placebo-controlled, randomized trials of MTX for the treatment of paediatric CD. However, the use of MTX in this population is increasing and the body of published observational studies is growing. Djuric et al (2018) provided a tabulated overview of 10 retrospective and 1 prospective studies that showed that MTX was effective in the maintenance of remission for 1 year, in 25–69% of thiopurine-resistant and thiopurineintolerant paediatric patients with CD (table on the next page). The only difference in the review by Djuric et al (2018) compared to Herfarth et al (2016) is the addition of the studies by Hosjak et al (2015) and Weiss et al (2009) in the overview of Djuric et al (2018)

Djuric et al (2018) conclude that MTX demonstrates high effectiveness as a second line immunomodulator in children with CD after thiopurine discontinuation. Although the initial experiences are encouraging, future prospective studies with a larger number of patients are needed to generate a definite conclusion, both on MTX effectiveness as a first line immunomodulator as well as on its efficacy in mucosal healing. Further studies should also clarify the optimal MTX dose and the route of administration in the case of concomitant use of MTX with anti-TNF agents in children.

Table 6 Effectiveness of Methotrexate in pediatric Crohn's disease (from Djuric et al (2018))

Reference	Number of centers/ Number of patients	Previous IS treatment	MTX treatment	Primary outcome	Remission rate
Mack et al. [25]	1/14	6MP	sc, qw	PCDAI≤10	50% at 3 mo
Uhlen et al. [26]	3/61	AZA	im (n-51), sc (n-10), qw	HBI≤4 CS-free Fistula closure	39% at 3 mo 49% at 6 mo 45% at 12 mo
Ravikumara et al. [27]	1/10	AZA	sc or im (n-9), po (n-1), qw	Symptom-free Normal IM	7 (70%) achieved remission
Turner et al. [28]	4/60	6MP/AZA	sc (n-43), po (n-5), sc→po (n-12), qw	PCDAI≤10 CS-free	42% at both 6 and 12 mo
Weiss et al. [29]	5/25	6MP/AZA (n-25) IFX (n-14, stopped in 11)	sc (n-19), po (n-6), qw	HBI≤4, CS-free No escalation of therapy (IFX)	16 (64%) achieved remission
Boyle et al. [30]	1/27	6MP/AZA	sc (n-26), po (n-1), qw	PGA CS-and IFX-free	48% at 6 mo 33% at 12 mo
Willot et al. [31]	1/63	6MP (n-61) IFX (n-16)	sc (n-61), im (n-1), po (n-1), qw	HBI<4, CS-free Fistula closure	29% at 3 mo 37% at 6 mo 25% at 12 mo
Sunseri et al. [6]	19/172	6MP/AZA (n-91) Without immunomodulators (n-81)	qw, mean dose 12.7 mg/m² (in remission), 12.4 mg/m² (not in remission)	PGA I, CS-, TP-, anti-TNF-free or surgery-free for>1 year	31% had sustained clinical remission
Turner et al. [19]	10/226	6MP/AZA (n-200) Without immunomodulators (n-26)	po (n-38), sc (n-90), qw sc→po (n-98)	PCDAI≤10 No fistula discharge at 6 and 12 mo No need for: CS, anti-TNF and surgery	34% had sustained CS-free remission
Haisma et al. [32]	10/131	6MP/AZA	sc (n-105), po (n-8), qw	PCDAI≤10 No need for CS, anti-TNF or EEN	52% at 12 mo
Hojsak et al. [7]	1/32	AZA	im, qw	PCDAI≤10 CS- and EEN-free MH (SES-CD: 0)	69% at 12 mo, 14 (44%) during whole follow-up (1–4.8 years), MH 8/14 (57%)

MTX: Methotrexate; 6MP: 6-mercaptopurine; AZA: Azathioprine; anti-TNF: Anti-tumor necrosis factor agent; IFX: Infliximab; po: Peroral; sc: Subcutaneous; im: Intramuscular; qw: Once weekly; MH: Mucosal healing; PCDAI: Pediatric Crohn's disease activity index; CS: Corticosteroid; EEN: Exclusive enteral nutrition; TP: Thiopurines; HBI: Harvey-Bradshaw index; PGA: Physician Global Assessment; IM: Inflammatory markers; mo: Months; IS: Immunosuppressive; SES-CD: Simple endoscopic score for Crohn's disease

Haisma et al (2015) identified consecutive children and teenagers with CD who were treated with MTX on second instance between 2002 and 2012. Those who used MTX primarily to treat a non-IBD indication (e.g. rheumatoid arthritis) and those on anti-TNF-alpha co-treatment were excluded from analysis. A total of 113 patients were eligible for inclusion, of which 42% were female. The median age at diagnosis was 13 years. Two thirds were initially treated with exclusive enteral nutrition, and AZA was the immunomodulator of choice (88%). MTX was initiated at a median age of 14 years and after a median disease duration of 2 years. Most common reason to start MTX was failure of TPs (n=73). Most patients received MTX subcutaneously (93%) at initiation, with a median dosage of 15mg/wk.

Eighteen months after introduction over 50% of the cohort was still using MTX. At 3, 6, 12 and 24 months, the proportions of patients with ongoing use of MTX were 94% (95% CI: 89 to 98), 83% (95% CI: 76 to 90), 65% (95% CI: 56 to 73) and 44% (95% CI: 35 to 54). A fifth of the cohort used MTX for more than 3 years.

The proportion of children with clinical benefit at 6, 12 and 24 months was respectively 73%, 52% and 29%. Four patients intentionally discontinued successful therapy before the end of the observation period. At the end of the observation period 11 patients still experienced clinical benefits on MTX monotherapy.

No differences in outcome were noted in patients who failed previous thiopurine therapy (66%) compared with those who did not tolerate TPs (34%). However, ineffectiveness of TPs did predict subsequent early MTX failure.

Supportive studies

Methotrexate for maintenance of remission in Crohn's disease

Feagan et al (2000) conducted a double-blind, placebo controlled, multicentre study of patients with chronically active CD who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. The aim of the study was to assess the effectiveness of MTX in maintaining remission in patients with CD. The patients were randomly assigned to receive weekly intramuscular injections of either 15 mg of methotrexate or placebo for 40 weeks. No other treatments for CD were permitted, excepting hydrocortisone ointment for perianal condition. The authors compared the efficacy of treatment by analysing the proportion of patients who remained in remission at week 40. Remission was defined as a score of ≤ 150 on the CDAI. Forty patients received methotrexate, and 36 received placebo. At week 40, 26 patients (65%) were in remission in the methotrexate group, as compared with 14 (39%) in the placebo group (p=0.04; absolute reduction in the risk of relapse, 26.1%; 95% CI, 4.4% to 47.8%). Fewer patients in the methotrexate group than in the placebo group required prednisone for relapse (11 of 40 [28%] vs. 21 of 36 [58%], p=0.01). None of the patients who received methotrexate had a severe adverse event; one patient in this group withdrew because of nausea. The conclusion of Feagan at al (2000) was that in patients with CD who enter remission after treatment with methotrexate, a low dose of methotrexate could maintain remission.

Another study by **Oren et al (1997)**, also compared methotrexate to placebo. They used oral methotrexate at a lower dose (12.5 mg weekly) and showed no difference between patients treated with methotrexate or placebo. The lower dose of methotrexate, oral route of administration, and small patient population may have been factors contributing to the lack of benefit seen with methotrexate.

An open label prospective study by **Lemann et al (2000)** evaluated the durability of MTX for maintenance of remission in a population of patients who had (mostly) failed or were intolerant to AZA and had already been treated with MTX for period of at least 6 months were followed for an additional 18 months. Out of 49 patients, 42 had previously failed AZA (85%). Out of the 41 achieving remission, 36 had previously failed AZA (87%). Most of the patients were administered 25 mg/wk im MTX, but some physicians changed the dose to oral administration, and some were even able to taper it. Despite some patients with oral MTX dosing and despite a heavy proportion of AZA failures, 71% of the study population remained in remission for 1 year and up to 52% remained in remission after 3 years. Among patients who initially did well on MTX after AZA failure, they were likely to remain well on that therapy over the next several years.

Two studies compared methotrexate to 6-mercaptopurine. **Maté-Jiménez et al (2000)** was a randomized, controlled trial that used oral methotrexate 10 mg weekly in patients that had achieved remission on a higher dose (15 mg orally weekly). When compared to patients treated with 6-mercaptopurine, there was no statistically significant difference with respect to maintenance of remission. **Oren et al (1997)** also did not show a statistically significant difference in continued remission between the methotrexate and 6-mercaptopurine groups.

The efficacy of oral MTX (10-20 mg po) for maintenance of remission in CD and ulcerative colitis was evaluated by a retrospective review by **Fraser et al (2002)**. Although one-year remission rates approached 90%, the data for CD and UC were combined and the clinical definition of remission was vague.

<u>Retrospective studies</u>

Wang et al (2018) A Chinese cohort retrospective study investigated the use of intramuscular MTX treatment in Chinese CD between January 2012 and December 2017. All patients had a history of AZA

use and intolerance to the drug or not achieving disease remission. Twenty-two (81.5%) patients received MTX treatment for at least 12 months. and 13 (48.1%) at 24 months. In the 14 (51.9%) patients who failed to maintain remission, 4 (14.8%) had a clinical response, 4 (14.8%) experienced relapse, and the other 6 (22.2%) discontinued MTX due to adverse events.

Huang et al (2017) performed a retrospective non-head-to-head controlled study assessing the efficacy and safety of MTX (20 mg/wk, subcutaneous) compared with TPs for refractory CD. Fifty-one consecutive patients who were refractory or intolerant to TPs and steroid-dependent were retrospectively analysed. The study concluded that MTX is effective in inducing and maintaining CR and achieving mucosal healing in patients with refractory CD, and its efficacy is comparable to that of TPs for naive patients.

Kopylov et al (2016) performed a retrospective cohort analysis, aimed to describe the efficacy of MTX for maintenance of remission in CD and to identify the factors associated with the probability of steroid- free clinical remission. A total of 49.2% of included patients were refractory or intolerant to TPs. The administration route for maintenance of clinical remission was intramuscular in 50.9% of patients. The study concluded that MTX treatment induced steroid-free clinical remission in over a third of CD patients and maintained it for a year in almost two-thirds of the responders.

Wahed et al (2009) evaluated clinical response of 99 CD patients retrospectively who were placed on MTX due to azathioprine (AZA) intolerance or nonresponse. The study suffers from a non-homogenous doses and method of administration of MTX for induction and maintenance. The range of induction dose of MTX was 2.5-25 mg/week and administration varied as either intra-muscular (IM) or per os (po). Improvement was based on multiple variables as available from the charts but was not standardised. With these caveats, clinical response occurred in 18 of 29 patients (62%) refractory to AZA/MP and 42 of 70 patients (60%) intolerant to AZA/MP. This suggests that MTX is effective in CD patients previously treated with AZA who experienced failure or nonresponse.

Case series:

Charpignon and Beau (2008) reported the experience of 35 patients with MTX administered parenterally at an induction dose of 25 mg per week for the first three months, then tapered to 15-25 mg per week, depending on the clinical response. Thirty-five patients with steroid-dependent CD were included in the study after failure of AZA in 34 cases. The rate of clinical remission was 50% at three months, 36% at six months, and 28% at one and two years. The rate of clinical response was 90% at three months, 56% at one year and 51% at two years. The rates of complete steroid withdrawal at three, six, 12 and 24 months in responders were, respectively: 39, 68, 69 and 100%. The efficacy of MTX was not statistically different among patients exhibiting AZA intolerance (47%, 8/17 patients) or no response (59%, 10/17 patients). The authors note that a fraction of patients appear to respond favourably to long-term MTX therapy, although the characteristic features of these potential responders have not been clearly identified.

Other supportive information

MAH included as support literature clinical guidelines for CD from European Crohn's and Colitis Organisation (ECCO) and American Gastroenterological Association (AGA) 2013. Both guidelines include methotrexate in the management of CD.

Two studies looked at the efficacy of methotrexate compared to azathioprine [Ardizzone (2003) in Mcdonald et al (2014)], 6-mercaptopurine [Maté-Jiménez et al (2000) in Mcdonald et al (2014)], and 5-ASA [Maté-Jiménez et al (2000) in Mcdonald et al (2014)]. These trials included small numbers of patients and the failure to show a difference between treatment groups may be due to a lack of statistical power. The statistically significant result favouring methotrexate over 5-ASA for induction of

remission reported by Maté-Jiménez et al (2000) needs to be interpreted with caution due to the small numbers of patients enrolled. According to Mcdonald et al (2014) none of these trials provide sufficient evidence to assess the efficacy of oral or intravenous methotrexate compared to other active medications used for the treatment of CD. To compare the relative efficacy of azathioprine and 6-mercaptopurine to methotrexate the randomization of large numbers of patients would be required.

Combination with Infliximab

Feagan et al (2014) conducted a 50-week double-blind, placebo-controlled trial (COMMIT) to evaluate potential superiority of combination therapy methotrexate-infliximab (IFX) over IFX alone in patients with Crohn's disease (CD). The study was conducted in 126 patients with CD who had initiated prednisone induction therapy (15-40 mg/day) within the preceding 6 weeks. Patients were assigned randomly to groups given methotrexate at an initial weekly dose of 10 mg, escalating to 25 mg week (n = 63), or placebo (n = 63). Both groups received IFX (5 mg/kg of body weight) at weeks 1, 3, 7, and 14, and every 8 weeks thereafter. Prednisone was tapered, beginning at week 1, and discontinued no later than week 14. The primary outcome was time to treatment failure, defined as a lack of prednisone-free remission (CD Activity Index, <150) at week 14 or failure to maintain remission through week 50. By week 50, the actuarial rate of treatment failure was 30.6% in the combination therapy group compared with 29.8% in the IFX monotherapy group (p = 0.63; hazard ratio, 1.16; 95% CI, 0.62-2.17). Prespecified subgroup analyses failed to show a benefit in patients with short disease duration or an increased level of C-reactive protein. No clinically meaningful differences were observed in secondary outcomes. Nevertheless, the MTX combination group did achieve statistically significant lower antibody levels (4% compared with 20%, p = 0.01) and demonstrated higher median serum trough levels of IFX (6.35µg/mL vs 3.75 µg/mL, p = 0.08). Whether this would result in fewer instances of infusion reactions or secondary non-response to IFX beyond 50 weeks remains to be seen. Combination therapy was well tolerated. The conclusion of Feagan et al (2014) was that the combination of infliximab and methotrexate, although safe, was no more effective than infliximab alone in patients with CD receiving treatment with prednisone.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH provided literature from studies showing efficacy for methotrexate in CD. The main limitation for most of the provided studies including Feagan in 1995 and 2000 is on the population included in the studies as these trials were conducted more than 20 years ago and before the introduction of biologics for the treatment of CD. The proposed dose and posology is based on the presented Feagan studies (1995 and 2000) i.e. for induction treatment: 25 mg/week administered subcutaneously, once patients have adequately responded to combination therapy, the corticosteroids should be tapered and for maintenance treatment: 15 mg/week administered subcutaneously, as monotherapy, if the patient has entered remission after 16 – 24 weeks of 25 mg methotrexate per week.

These studies included a steroid dependent population and were designed in the early 90s.

Feagan et al 1995 study was a double-blind, placebo-controlled multicentre study of weekly injections of methotrexate in patients who had chronically active CD despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. The primary outcome measure was clinical remission at the end of the 16-week trial.

As a placebo-controlled trial, using a parenteral methotrexate solution the trial included an adequate number of patients and the trials duration can be considered acceptable as such for demonstrating induction of remission in CD. The dose supports the proposed posology. However, the CHMP noted that CD treatment, namely induction of remission has changed in recent years with use of monoclonal antibodies, so the population included in this study as "chronically active after prednisolone" may be different from the present CD population.

Feagan et al (2000) conducted a double-blind, placebo controlled, multicentre study of patients with chronically active CD who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. The aim of the study was to assess the effectiveness of MTX in maintaining remission in patients with CD. This study could be considered suitable to support the use of MTX for maintenance of remission.

The remaining data come only from observational studies found in peer reviewed literature. Moreover, the paediatric studies provided do not include any RCT being only small open label studies, case series or retrospective studies. The CHMP therefore considered that they were inadequate to provide reliable evidence of efficacy in this population.

Further submitted literature review included more recent retrospective studies and case series that are intended to support MTX use in CD. These studies used parenteral MTX for induction of remission in the proposed dose ranges but due to the use in mild disease and various second line settings and the open-label design these studies do not provide sufficient evidence for MTX benefit.

Efficacy data and additional analyses

The only RCT data on the use of parenteral methotrexate in Crohn's disease patients refractory or intolerant to thiopurines come from a single publication from Feagan et al., 1995. This was a double-blind, placebo-controlled multicenter study of weekly injections of methotrexate in a group of patients with chronically active Crohn's disease, showing that methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone. The study was conducted in patients who had chronically active Crohn's disease despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (94 patients) or placebo (47 patients). 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 than those in the placebo group (P=0.026). The mean score on the Crohn's Disease Activity Index after 16 weeks of treatment was significantly lower in the methotrexate group (162) than in the placebo group (204, P=0.002). [Feagan et al (1995)].

The indication applied for was "*treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to* thiopurines".

Considering the population included in this study (patients who had chronically active CD despite a minimum of three months of prednisone therapy), the CHMP was of the opinion that the use of MTX in induction of remission in Crohn´s disease was only supported in steroid treated patients, trying to decrease the steroid dose. In particular, the CHMP considered that no claim could be supported for use of MTX as monotherapy in induction of remission in Crohn´s disease.

The CHMP also noted that the recent revision of the recommendations of the European Crohn's and Colitis Organisation (ECCO) from 2020 (Torres et al., 2020) now excludes the use of parenteral methotrexate for induction of remission as well as thiopurines as the positive effects (induction of

remission and only in combination with steroids) could not be definitely attributed to treatment with parenteral Methotrexate given as add-on therapy on top of 12.5-40 mg/day prednisone. Still, the guideline acknowledges "however MTX may be considered as an option in steroid-dependent patients with moderate to severe disease when alternative options (including surgery) cannot be used." Parenteral MTX is still included in the recommendations for maintenance treatment. Furthermore, the ACG guideline reviewed in 2018, includes parenteral methotrexate therapy as effective to maintain remission in steroid-dependent moderate to severe CD.

The CHMP also noted that based in the current evidence and available treatment options, as proposed in the ECCO 2020 guideline, MTX may be considered for induction of remission "as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used."

The population included also seems more steroid resistant than "thiopurine intolerant or resistant". The recent Feagan et al 2014 study did not confirm any benefit of the association of Infliximab with methotrexate besides a lower level of antibodies in the IFX+ MTX arm. In this context it should be noted, that the medical need in the indication of CD has changed considerably in the recent years. While, there were no/limited alternatives in the population with failed thiopurines treatment before the treatment with biologics became broadly available variable treatment options are available today. Thus, the place of pMTX in the treatment of CD has narrowed considering the broad spectrum of treatment options.

In line with the above and at the CHMP's request, the MAH amended the first part of the claimed indication to "Induction of remission in moderate steroid-dependent Crohn's disease in adult patients, in combination with corticosteroids".

[Feagan et al (2000)] was a double-blind, placebo-controlled, multicenter study of patients with chronically active Crohn's disease. The study showed that a low dose of methotrexate maintains remission. The study included patients who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for Crohn's disease were permitted. Of the included patients, 40 received methotrexate, and 36 received placebo. At week 40, 26 patients (65%) were in remission in the methotrexate group, as compared with 14 (39%) in the placebo group (P=0.04). Fewer patients in the methotrexate group than in the placebo group required prednisone for relapse (28% versus 58%, P=0.01).

The study Feagan, 2000 included only 76 patients that had previously responded to MTX 25mg/ week. Patients were given either methotrexate 15 mg/week intramuscularly (n = 40) or identical placebo (n = 36) for a total of 40 weeks. The primary outcome measure was the occurrence of relapse at 40 weeks; secondary outcomes included the need for prednisone and adverse drug reactions. The patients were assessed every 4 weeks for a total of 40 weeks. The study medication was discontinued if a patient required treatment for active Crohn's disease. However, of the 36 patients that relapsed in the study, 22 were previously given methotrexate 25 mg intramuscularly once weekly, in addition to prednisone for treatment of an exacerbation. As such maintenance of remission should only be accepted for patients who have responded to MTX in the induction of remission phase.

In line with the data above and at the CHMP's request, the MAH amended the second part of the indication on maintenance of remission to "as monotherapy, in patients who have responded to methotrexate".

Two other trials [(Oren et al (1997); Arora et al (1999) in Mcdonald et al (2014)] showed no statistically significant difference between low dose oral methotrexate and placebo treated patients. These trials may have failed to show a benefit of methotrexate in refractory CD because they used lower doses of the drug (12.5 to 15 mg/week compared to 25 mg/ week) and oral administration. Both studies included relatively small numbers of patients and the failure to show a difference between the treatment and control groups may have been due to insufficient statistical power. It is noted that Oren et al and Arora et al studies were evaluated in the Cochrane review and classified as low evidence due to the small numbers of patients included. The CHMP acknowledged that methotrexate oral formulation in lower dose was used in both studies.

Studies from the paediatric population were also submitted by the Applicant. These data confirm that MTX is being used but most of the data are open-label series, retrospective, non-randomised, non-controlled studies in variable population, with variable prior/concomitant treatments, variable doses of MTX and routes of administration applied. Based on such heterogeneous data, the CHMP was of the opinion that no conclusions can be drawn for dosage, route of administration and CD paediatric population. Consequently, the CHMP concluded that the use of Nordimet for treatment of CD in paediatric population is not recommended. The MAH agreed to amend the product information accordingly.

2.4.4. Conclusions on the clinical efficacy

The proposed dose and posology is based on the presented Feagan studies (1995 and 2000). These studies included a steroid dependent population and were designed in the early 90s, most of the patients had not used thiopurines.

Patients included in these main studies do not represent the proposed population to be included in the indication, i. e. "mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines". Patients included in Feagan et al (1995) on induction of remission had chronically active CD despite a minimum of three months of prednisone therapy accordingly the trial can only be used to support MTX treatment in steroid treated patients, trying to decrease the steroid dose. In particular, no claim could be supported for its use as monotherapy. It is also noted that based in the current evidence and available treatment options, as proposed in the ECCO 2020 guideline, MTX may be considered for induction of remission "as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used."

Furthermore, there is no mentioning of the "response status" or "tolerability status" to thiopurines" and the statement "refractory or intolerant to thiopurines" was deleted from the claimed indication accordingly.

[Feagan et al (2000)] which included 76 patients that had previously responded to MTX 25mg/ week showed that low dose of methotrexate maintains remission in CD. In this study patients were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for Crohn's disease were permitted. As such, the CHMP considered that the indication can only be accepted on maintenance of remission for patients who have responded to MTX in the induction of remission phase.

Studies in paediatric patients confirmed that MTX is being used but most of the data are open-label series, retrospective, non-randomised, non-controlled studies in variable population, with variable prior/concomitant treatments, variable doses of MTX and routes of administration applied. Based on such heterogeneous data, no conclusions can be drawn for dosage, route of administration and CD

paediatric population. Consequently, the CHMP concluded that the use of Nordimet for treatment of CD in paediatric population is not recommended.

Based on above considerations and at the CHMP's request, the MAH agreed to amend the indication as follows:

"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."

This revised indication was considered acceptable considering the submitted data on efficacy.

2.5. Clinical safety

Introduction

In general, the incidence and severity of acute side effects of methotrexate are related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs. The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may show an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity and have led to eventual death. Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation.

Patient exposure

The application was based on scientific literature.

Adverse events

Chande et al (2011) performed a retrospective chart review of CD patients in their practice treated with methotrexate. Data related to the safety and tolerance of methotrexate was extracted and analysed. Of 92 patients treated with methotrexate, there was enough data for 79 patients for analysis (49 women and 30 men; mean age 28.8 years). Forty- two patients (53%) had previously received azathioprine. Overall, 40 patients (51%) achieved and maintained remission on methotrexate, including 13 of 30 (43%) who concomitantly received anti-TNF therapy. The mean total accumulated dose of methotrexate was 1727 mg [SD 1572 mg], with a mean total duration of methotrexate use of 25.4 months (SD 43.1 months). The most common adverse events were nausea (22%) and elevated liver enzymes (10%). Only 6% of patients stopped methotrexate therapy because of persistently abnormal liver enzymes. No patients underwent liver biopsy.

Feagan et al (1995) showed in their landmark randomized controlled trial that adverse events were observed in approximately equal frequency in the methotrexate treated (45%) and control (42%) groups. However, 17% of the methotrexate treated patients were withdrawn from treatment because of adverse events, compared to 2% in the placebo group ($p = 0.012$). The most common reasons for withdrawal were nausea and vomiting (6 patients) and asymptomatic elevation of liver enzymes (7 patients). No serious adverse effects were observed. Although the design of this study resulted in withdrawal of these patients, in clinical practice in patients with rheumatoid disease, adverse effects such as nausea are often dealt with or prevented by the concomitant administration of folic acid [Griffith et al (2000), Lorenzi et al (2000) in McDonald et al (2014)], and asymptomatic elevations of transaminases are not considered to reflect or predict existing or future hepatic disease [Kremer et al (1994) in McDonald et al (2014)].

In Feagan et al (2000) study there were no severe adverse events reported in the methotrexate group. In the three trials that employed lower doses of oral methotrexate no serious adverse effects were observed [Arora et al (1999); Maté-Jiménez et al (2000); Oren et al (1997)]. However, in one trial ALT levels were increased in 53% of patients receiving methotrexate, compared to 22% of patients receiving placebo [Arora et al (1999)]. No clinically significant hepatotoxicity was observed in any patient.

Schröder et al [2003] provided a literature overview of the use of low-dose methotrexate, including a discussion on the toxicity of low-dose methotrexate. According to Schröder et al [2003], frequency and severity of adverse effects during low dose MTX therapy in irritable bowel disease (IBD) are relatively small, requiring withdrawal of medication in approximately 10% of patients (table below). The most common adverse effects of low dose MTX therapy for IBD include GI symptoms (nausea and vomiting, diarrhoea, abdominal distension and pain), elevated serum transaminases, central nervous system effects, and infections. Most side effects are transient and resolve with either continuation of therapy or dose reduction.

Table 7 ***Details of adverse events occurring on more than one occasion in trials of low dose methotrexate in the treatment of 465 patients with IBD [Schröder et al (2003)]***

Adverse Events	Incidence*	Withdrawn From Study/Medication
Frequent		
Nausea and vomiting	104 (22.4%)	16
Infections	59 (12.7%)	4
Cold	32 (6.9%)	
Influenza-like symptoms	16 (3.4%)	
Fever and chills	4 (0.9%)	
Pneumonia	5 (1.1%)	
Herpes zoster	2 (0.4%)	
Headache	39 (8.4%)	3
Abnormal liver function test	35 (7.5%)	10
Fatigue	27 (5.8%)	0
Less frequent		
Arthralgia/myalgia	22 (4.7%)	0
Pain	18 (3.9%)	2
Abdominal	14 (3.0%)	
Chest	2 (0.4%)	
Other	2 (0.4%)	
Diarrhea	13 (2.8%)	2
Rash	13 (2.8%)	2
Stomatitis	9 (2.0%)	1
Rare		
Abdominal bloating/distension	8 (1.7%)	0
Leukopenia	7 (1.5%)	4
Alpecia	5 (1.1%)	0
Paresthesia	5 (1.1%)	0
Insomnia	4 (0.9%)	0
Anorexia	3 (0.6%)	0
Pneumonitis	2 (0.4%)	2
Death of unknown origin	2 (0.4%)	2
Others (n = 1)	68 (14.6%)	1

Data based on Refs. 35–43, 45–47.
* = number of patients (% of patients).

Conway et al (2015) performed a systematic literature review, and a meta-analysis of randomised controlled trials on patients with inflammatory bowel disease, psoriasis, and psoriatic arthritis. The authors had the aim to evaluate the relative risk of pulmonary disease among patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with methotrexate. The inclusion criteria for study selection were: double blind randomised controlled trials; patients with psoriasis, psoriatic arthritis, or inflammatory bowel disease; studies in English; studies consisting of a minimum of two arms, at least one receiving methotrexate and at least one not receiving methotrexate; studies including only adults (≥18 years); trials of 12 weeks or more duration; studies of 50 patients or more; and studies reporting respiratory side effects for methotrexate and comparator groups separately. Seven studies met the inclusion criteria, six with placebo as the comparator. Overall, 504 respiratory adverse events were documented in 1630 participants. Methotrexate was not associated with an increased risk of adverse respiratory events (relative risk 1.03, 95% confidence interval CI 0.90 to 1.17), respiratory infections (1.02, 0.88 to 1.19), or non-infectious respiratory events (1.07, 0.58 to 1.96). No pulmonary deaths occurred.

According to the European Crohn's and Colitis Organisation (ECCO) practical guidelines for CD management [Dignass et al (2010)], early toxicity from methotrexate is primarily gastrointestinal (nausea, vomiting, diarrhoea and stomatitis) and can be limited by co-prescription of folic acid 5 mg two or three days apart from the methotrexate. Treatment is discontinued in 10–18% of patients because of side-effects (Fraser et al. 2003).

A study of liver biopsies in IBD patients taking methotrexate showed only mild histologic abnormalities, despite cumulative doses of up to 5410 mg [Te et al (2000)]. Surveillance liver biopsy is not warranted, but if the AST doubles then it is sensible to withhold methotrexate until it returns to normal

before a rechallenge. The prevalence of pneumonitis has been estimated to be 2–3 cases per 100 patients-years of exposure, but large series have not reported any cases (Fraser et al. 2003).

Table 8 Adult population with Crohn's disease (observational studies)

Adult population with Crohn's disease (observational studies)

	Patients on MTX	ADE frequency	Specific ADEs	Discontinuations due to ADEs
Wang et al (2018)*	22	10 (37%)	GI side effects (6) Leucopenia (2) Pneumonia (1) Local muscle pain (1)	8 (30%)
Huang et al (2017)	51	15 (29%)	Leukopenia (6) Hepatotoxicity (6) Headache, arthralgia, and myalgia (1) Rash (1) Alopecia (1)	7 (14%)
Lemann et al (2000)	49	22 (49%)	Liver abnormalities (10) Nausea and vomiting (6) Headache (5) Paresthesia (1) Skin rash (1) Alopecia (1) Pneumonitis(1) Death (unknown origin, 1)	5 (10%)
Kopylov et al (2016)	118	34 (29%)	Nausea (13) Liver toxicity (8) Pancytopenia (1) Flu-like symptoms (5) GI intolerance (11) Infection (1) Unspecified (7)	19 (16%)
Wahed et al (2009)*	131	23 (17%)	Abnormal liver function tests (8) Respiratory (5) Bone marrow suppression (4) Nausea and vomiting (3) Hair loss (2) Nonspecific (3	11 (8%)
Charpignon and Beau (2008)*	35	9 (26%)	GI disorders (3) Elevated liver enzymes (4) Medullary aplasia after combination with dipyrone (1) Allergic lung disease (1)	6 (17%)
Chande et al (2011)*	79	42 (53%)	Nausea (17) Vomiting (3) Headache (5) Elevated liver enzymes (8) Pruritic skin rash (2) Abdominal bloating (2) Mouth ulcers (3) Pancytopenia (1) Diarrhea (1)	5 (6%)

*all or part of the study population received folic acid

Table 9 Paediatric population with IBD, including Crohn's disease (observational studies):

Paediatric population with IBD, including Crohn's disease (observational studies)

	Patients on MTX	ADE frequency	Specific ADEs	Discontinuations due to ADEs
Mack et al (1998)*	14	n.r.	Nausea Headaches	2 (14%)
Turner et al (2007)*	60	35 (58%)	Transient ELE (16) Persistent ELE (9) Nausea (10) Local injection reactions (2) Hypersensitivity reaction (2) Transient neutropenia (2) Transient thrombocytopenia (1) Serious infection (1) Headache (1)	8 (13%)
Uhlen et al (2006)*	61	14 (24%)	Nausea and vomiting (7) Infection complication (1) Transaminitis (2) General asthenia (4)	6 (10%)
Haisma et al (2015)	113	68 (60%)	Nausea and vomiting Fear of needle sticks Need for antibiotics Abdominal pain Headache Pain at injection site Transient transaminitis	21 (19%)
Boyle et al (2010)	27	16 (60%)	Nausea (7) Transient transaminase elevation (4) Leukopenia (2) Headache (1) Fatigue (2)	1 (4%)
Willot et al (2011)*	93	46 (49%)	Nausea and/or vomiting (21) Elevated liver enzymes (10) Cytopenia: - thrombopenia (2) - leukopenia (9) Other (4)	13 (14%)
Ravikumara et al (2007)*	10	3 (39%)	Transient increase of alanine Aminotransferase (1) Neutropenia (1) Dry mouth and sore throat (1)	0 (0%)
Sunseri et al (2014)	172	57 (33%)	Rash Abdominal pain Shortness of breath Nausea Vomiting Fatigue Alopecia ALT > 60 IU/L (26) Leucopenia (21)	14 (8%)
Weiss et al (2009)*	25	6 (24%)	Nausea and vomiting (3) persistently elevated hepatic enzymes (2) Pancreatitis (1)	4 (16%)
Hojsak et al (2015)	32	6 (18.8%)	Nausea (3), Headache (2) Elevated liver enzymes (1)	1 (3%)

n.r. = not reported, ELE = elevated liver enzymes, *all or part of the study population received folic acid

The safety profile of MTX in Crohn's disease seems to be consistent with other indications [McDonald et al (2014); Patel et al (2014)].

2.5.1. Discussion on clinical safety

Methotrexate side-effects incidence and severity may be acute, related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the

target organs. The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leukopenia, thrombocytopenia, and anaemia may all occur. Long term side-effects besides vigilance of haematological values are mainly GI related: nausea, elevated liver enzymes and progression to fibrosis. Pulmonary side-effects are also known. The proposed dose is within the posology for the other therapeutic indications. Data included in the proposed population included in the indication are mainly from case series and retrospective studies.

The MAH provided an extended review based on the available data for CD in adults and children. The studies presented support a similar safety profile in the proposed indication. The CHMP considered that the information in the product information adequately describes the safety profile. The MAH took the opportunity to delete from the package leaflet the influenza vaccine from the examples of live vaccines as most influenza vaccines are not live vaccines.

The MAH submitted an updated RMP version v5.3 with this application. Among other changes, the combination of the products Nordimet (EMEA/H/C/00398) and Imeth (NL/H/2607/001-008/MR) into a single EU RMP was proposed with this version.

In view of the well-established safety profile and long-term experience with the use of methotrexate, the MAH was requested to delete the following important/potential risks from the RMP:

- Increased risk of neoplasia
- Bone growth defects in the paediatric population
- Progressive Multifocal Leukoencephalopathy

("Lymphoma" is considered included in "increased risk of neoplasia". It can therefore also be deleted from the list of safety concerns.)

The above mentioned risks do not require additional pharmacovigilance activities. The important risk (Increased risk of neoplasia) and potential risks (Bone growth defects in the paediatric population, Progressive Multifocal Leukoencephalopathy) will be assessed within future PSUSA procedures.

Additionally, the following was aligned in the updated RMP:

- "Leukoencephalopathia" was deleted from important identified risks.
- "Medication error, including overdose from inadvertent daily instead of weekly dosing" was reworded to "Medication errors due to inadvertent daily instead of once weekly dosing".

During the assessment it was noted that the RMP of Imeth states that "intestinal perforation" is included as a warning in the SmPC but not for Nordimet and the applicant was asked for clarification. The company clarified that there are no non-clinical findings confirmed by clinical data. In the MAHs safety database, one case was retrieved corresponding to one event (PT= diverticular perforation). This event was serious due to hospitalization criteria. The outcome was recovered with sequelae. The MAH assessed this event as possibly related to methotrexate; however, other etiologies cannot be ruled out (e.g relevant history included sickle cell disease).

This case report was not considered strong evidence of causal relationship and a pharmaco-epidemiological study performed by Curtis et al (2011) investigated the incidence of GI perforation in patients with RA using a database of a large US health plan. They assessed the rate of GIP in relation to a variety of medications commonly used for the treatment of RA. Among 40,841 RA patients, 37 hospitalizations with GI perforation were identified. The rate of GI perforation among current biologic users concomitantly exposed to oral glucocorticoids was higher (rate=1.12 per 1,000 patient-years, 95% CI 0.50, 2.49) than for biologic users who were not glucocorticoid users (rate=0.47 per 1000

patient-years , 95% CI 0.22, 0.98) or MTX users using glucocorticoids (rate=0.87 per 1000 patient-years , 95% CI 0.36, 2.10). Neither biologics nor MTX were significantly associated with perforation, in contrast to current use of glucocorticoids and NSAIDs together (hazard ratio =4.7, 95% CI 1.9, 12.0) or glucocorticoids alone (hazard ratio=2.8, 95% CI 1.3, 6.1). Diverticulitis also was a strong risk factor (hazard ratio = 9.1, 95% CI 3.1, 26.4). Seventy percent of perforation cases used glucocorticoids, had antecedent diverticulitis, or both. A majority of patients were either glucocorticoid users or had previously recognized diverticulitis, these individuals should be considered at higher risk. Whilst no causal association with methotrexate can be concluded the MAH proposed to align the existing warning on diarrhea and stomatitis following dehydration with the SmPC of other MTX containing products adding in 4.4 "*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."* which was endorsed by the CHMP. No additional information on intestinal perforation was included in section 4.8 of the SmPC, which was acceptable to the CHMP as it is in line with other MTX containing products.

Additionally, the RMP was updated with information on the DHPC as circulated after the Referral procedure EMEA/H/A-31/1463 as an additional Risk minimization measure which was considered acceptable.

The posology section for children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis includes a statement that the safety and efficacy of Nordimet in children < 3 years of age have not been established and that no data are available. Accordingly, the MAH added the use in children < 3 years as missing information for the therapy of polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) in the RMP. This point should be further monitored by routine pharmacovigilance. The respective data should be provided and discussed in future PSURs, especially with regards to whether the safety profile differs from that characterized so far. At the CHMP request, section 4.4 of the SmPC was aligned to include the following information: "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)."

2.5.2. Conclusions on clinical safety

Methotrexates known side-effects incidence and severity may be acute, related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs. The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leukopenia, thrombocytopenia, and anaemia may all occur. Long term side-effects besides vigilance of haematological values are mainly GI related: nausea, elevated liver enzymes and progression to fibrosis. Pulmonary side-effects are also known. The proposed dose is within the posology for the other therapeutic indications.

The data submitted with the present application are mainly from retrospective studies and case series; however, based on the extended review of available data for CD provided a similar safety profile in the indication "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" can be concluded. The CHMP considered that the information in the product information adequately describes the safety profile.

2.5.3. PSUR cycle

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. Risk management plan

The MAH submitted an updated RMP version v5.3 with this application. The main proposed RMP changes were the following:

- Update of RMP in line with the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011 Rev 2) including review of safety concerns.
- Combination of the products Nordimet (EMEA/H/C/00398) and Imeth (NL/H/2607/001-008/MR) into a single EU RMP.
- Inclusion of a new indication for Nordimet: Mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines.
- Addition of risk minimisation measures as an outcome of the methotrexate Referral procedure (EMEA/H/A-31/1463) regarding medication errors.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Haematological toxicity
	Hepatotoxicity
	Pulmonary toxicity
	Renal toxicity
	Medication error due to inadvertent daily instead of once weekly dosing
Important potential risks	none
Missing information	Exposure in children younger than 3 years old

Pharmacovigilance plan

Routine pharmacovigilance activities
Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for the following risk: medication error including overdose from inadvertent daily instead of

weekly dosing.

• A targeted follow-up questionnaire for this risk will be sent to reporters (see Annex 4). Only those questions from the form should be sent to the reporter which ask for information not yet provided in the initial report. Alternatively, the reporter should be provided with a pre-filled form already including the information initially provided.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for other risks.

Additional pharmacovigilance activities
No additional pharmacovigilance activities.

Summary Table of additional Pharmacovigilance activities
None.

Risk minimisation measures

Important identified risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Haematological toxicity	Routine risk minimization measures Warning in sections 4.4, 4.5 and 4.8 of the SmPC Contraindication in section 4.3 of the SmPC Warning in section 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hepatotoxicity	Routine risk minimization measures Warning in sections 4.2, 4.4, 4.5 and 4.8 of the SmPC Contraindication in section 4.3 of the SmPC Warning in section 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None. Additional pharmacovigilance activities: None.
Pulmonary toxicity	Routine risk minimization measures Warning in sections 4.4 and 4.8 of the SmPC Warning in sections 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None. Additional pharmacovigilance activities: None.
Renal toxicity	Routine risk minimization measures Warning in sections 4.2, 4.3, 4.4 and 4.8 of the SmPC Warning in sections 2 and 4 of the PL	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None. Additional pharmacovigilance activities:

	Restricted medical prescription Additional risk minimization measures: None	None.
Medication errors due to inadvertent daily instead of once weekly dosing	Routine risk minimization measures Boxed warning in section 4.2 of the SmPC Warning in sections 4.4 and 4.8 of the SmPC Warning in sections 2 and 3 of the PL Restricted medical prescription Additional risk minimization measures: DHPC communication (see annex 6)	Routine pharmacovigilance activities beyond ADR reporting and signal detection A targeted follow-up questionnaire for medication errors
Missing information		
Safety concern	**Routine risk minimization measures**	**Pharmacovigilance activities**
Missing information Exposure in children younger than 3 years old	Routine risk communication Limited guidance in sections 4.2 and 4.4 of the SmPC Warning in sections 2 and 3 of the PL Restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Please refer to the full updated PI for details.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Leaflets are sufficiently similar concerning content and layout.

No full user consultation with target patient groups on the package leaflet has been performed on the

basis of a bridging report making reference to Nordimet PEN. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH claimed an indication for methotrexate solution for injection in the "treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines".

The dosing recommendations were as follows:

Dosage in adult patients with Crohn's disease:

- Induction treatment: 25 mg/week administered subcutaneously.

Response to treatment can be expected after approximately 8 to 12 weeks.

- Maintenance treatment: 15 mg/week administered subcutaneously.

Dosage in children and adolescents with Crohn's disease:

- Induction treatment: 15 mg/m2 BSA/week to a maximum of 25 mg administered subcutaneously.

Response to treatment can be expected after approximately 8 to 12 weeks.

- Maintenance treatment: Children: 10 mg/ m2 BSA/week to a maximum of 15 mg administered subcutaneously.

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

CD is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. Some patients may have a continuously clinically active disease.

Nordimet, was authorised 18/08/2016 as a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC referring to the reference product Lantarel FS 25mg/ml from Pfizer Pharma GmbH. Nordimet is supplied in prefilled pens for subcutaneous use containing volumes ranging from 0.3 to 1ml. One ml of solution contains 25 mg of methotrexate.

3.1.2. Available therapies and unmet medical need

Remission in CD can be achieved either by medical treatment or surgery. Medical therapy recommended by clinical guidelines includes corticosteroids, immunosuppressant drugs and biologics (anti-tumour necrosis factor (TNF) α agents and adhesion molecule inhibitors).

Thiopurines are used for induction of remission in milder patients, maintenance therapy and association with biologics for induction of remission. Methotrexate is used as a second line agent for induction of remission when other alternatives cannot be used and for maintenance of remission in

steroid dependent CD. For moderate to severe patients induction of remission is recommended with biologics.

Methotrexate parenterally has been included in clinical guidelines as a second line option (ACG) but the more recent guidelines from ECCO 2020 (Torres et al) only includes a reference for its use in moderate to severe disease, for induction of clinical remission when other alternatives cannot be used and for maintenance of remission in patients with steroid-dependent CD, due to an increased number of medicines approved for CD.

3.1.3. Main clinical studies

This application is solely based on published literature. The pivotal evidence provided is based on two publications:

Feagan et al 1995 study was a double-blind, placebo-controlled multicentre study of weekly injections of methotrexate in patients who had chronically active CD despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. The primary outcome measure was clinical remission at the end of the 16-week trial.

Feagan et al (2000) was a double-blind, placebo controlled, multicentre study of patients with chronically active CD who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. The aim of the study was to assess the effectiveness of MTX in maintaining remission in patients with CD.

3.2. Favourable effects

Feagan et al (1995) showed that methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone. The study was conducted in patients who had chronically active Crohn's disease despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (94 patients) or placebo (47 patients). 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 than those in the placebo group (P=0.026). The mean score on the Crohn's Disease Activity Index after 16 weeks of treatment was significantly lower in the methotrexate group (162) than in the placebo group (204, P=0.002).

Feagan et al (2000) showed that a low dose of methotrexate maintains remission. The study included patients who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for Crohn's disease were permitted. Of the included patients, 40 received methotrexate, and 36 received placebo. At week 40, 26 patients (65%) were in remission in the methotrexate group, as compared with 14 (39%) in the placebo group (P=0.04). Fewer patients in the methotrexate group than in the placebo group required prednisone for relapse (28% versus 58%, P=0.01).

3.3. Uncertainties and limitations about favourable effects

Efficacy of methotrexate in Crohn´s disease is mainly based in small studies or studies started in the 90s. A double blind placebo-controlled trial, multicentre and randomized (Feagan et al 1995) is submitted as the pivotal basis for this application in induction therapy, and a similarly sized study (Feagan et al 2000) is submitted as the pivotal basis for this application in maintenance therapy. These studies included a steroid dependent population and were designed in the early 90s. Patients were requested not to take immunosuppressives concomitantly (presumably due to the increased risks associated with dual immunosuppression), but there is no mentioning of the "response status" or "tolerability status" to thiopurines.

Patient enrolled in the study by **Feagan et al., 1995** had chronically active Crohn's disease despite a minimum of three months of prednisone therapy. A claim on monotherapy can therefore not supported based on this data.

Patient enrolled in the study by **Feagan et al 2000** had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. No other treatments for Crohn's disease were permitted. Accordingly, the study can only support an indication in patients who have responded to MTX in the induction of remission phase.

The population included also seems more steroid resistant than "thiopurine intolerant or resistant". The recent Feagan et al 2014 study did not confirm any benefit of the association of Infliximab with methotrexate besides a lower level of antibodies in the IFX+ MTX arm. In this context it should be noted, that the medical need in the indication of CD has changed considerably in the recent years. While, there were no/limited alternatives in the population with failed thiopurines treatment before the treatment with biologics became broadly available variable treatment options are available today. Thus, the place of pMTX in the treatment of CD has narrowed considering the broad spectrum of treatment options.

Several other studies submitted used methotrexate but with different administration routes (ev and oral) inferior dose and with mixed population included most of them with small numbers. Most of the patients were treated with steroids, with variation in dosages.

Studies from the paediatric population have also been included confirming that MTX is being used but most of the data are open-label series, retrospective, non-randomised, non-controlled studies in variable population, with variable prior/concomitant treatments, variable doses of MTX and routes of administration applied. Based on such heterogeneous data, no conclusions can be drawn for dosage, route of administration and CD paediatric population.

3.4. Unfavourable effects

Methotrexate known side-effects incidence and severity may be acute, related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs. The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leukopenia, thrombocytopenia, and anaemia may all occur. Long term side-effects besides vigilance of haematological values are mainly GI related: nausea, elevated liver enzymes and progression to fibrosis. Pulmonary side-effects are also known. The proposed dose is within the posology for the other therapeutic indications. Data included in the proposed population included in the indication are mainly from case series and retrospective studies.

The MAH provided an extended review based on the available data for CD. The studies presented due

support to a similar safety profile in the proposed indication.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of Methotrexate is well-established.

3.6. Effects Table

Table 10 Effects Table for Nordimet.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Remission	Decrease in CDAI and increased in quality of life IBDQ		MTX 25mg IM/ week	Placebo	Steroid dose at beginning is increased in some patients	Feagan, 1995 Feagan 2000
Decrease in steroid dose	Mean dose decreased			Placebo		Feagan, 1995
	Decreased relapses				Fewer patients in the MTX group required prednisolone for the relapse 28% vs 58%.	Feagan 2000
Unfavourable Effects						
Side-effects	Nausea, vomiting, diarrhea					Feagan, 1995
Lack of efficacy			MTX oral		Non-significant results in several studies due to bias	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Methotrexate Nordimet has been approved as a Hybrid application for treatment of RA, Psoriasis when a systemic therapy is needed and polyarticular arthritis. The reference product is Lanctarel, Pfizer. The MAH has applied for an extension of Indication to include the treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines. The reference product does not have this indication and this application is based on submitted literature.

Methotrexate in parenteral dosing has been used since de 90s and similar methotrexate parenteral formulations authorised in the EU have an indication in the treatment of Crohn’s disease.

The data presented by the MAH are mostly from old studies and no RCT completely reflects the proposed indication. Design of most of the studies is limited either by the numbers of patients included or by bias such as steroid dosage. Data in children are very heterogeneous and lack robust evidence. Most of the studies are case series or retrospective studies from the literature. Detailed review of safety data in the proposed indication based on literature was provided and confirmed the well-known safety profile of Methotrexate containing products.

The CHMP considered that the evidence provided is far from robust: pivotal trials (reported by Feagan et al) are from 1995 and 2000 and the standard of care changed in the recent years. The current ECCO guideline (Torres et al., 2020) excludes MTX but keeps the possibility of its use in a population "steroid-dependent, moderate to severe with no indication for surgery". The same guideline removes tiopurines as induction of remission therapy. The British guidelines from the Society of Gastroenterology (Lamb et al, Gut, 2019) still recommend MTX for induction of remission and maintenance of remission.

The CHMP considered that the indication claim "in patients intolerant or refractory to thiopurines" has not been justified based on submitted data. Patients in the Feagan studies (Feagan et al 1995 and 2000) were requested not to take immunosuppressives concomitantly (presumably due to the increased risks associated with dual immunosuppression), but there is no mentioning of the "response status" or "tolerability status" to thiopurines. Furthermore, the patients were classified as corticosteroid resistant/dependent based on the concomitant steroid dose received. In the maintenance study Feagen et al (2000) the same patients were treated with MTX monotherapy after achieving remission with a combined MTX/corticosteroid treatment.

The paediatric studies provided do not include any RCT being only small open label studies, case series or retrospective studies, which does not support the use of MTX for the treatment of paediatric population with Crohn's Disease.

The CHMP was of the opinion that the claimed indication *"mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines*" was not justified based on the results and the study conditions (patient population, concomitant medication) of the pivotal studies by Feagan et al (1995, 2000).

However, the CHMP acknowledged that the pivotal studies did show efficacy in the population studied which was comprised of adult patients who had moderate chronically active Crohn's disease despite a minimum of three months of prednisone therapy during induction and were treated for maintenance with MTX without other treatments for Crohn's disease permitted.

In line with the above and at the CHMP's request, the MAH agreed to amend the indication as follows:

"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"

3.7.2. Balance of benefits and risks

Based on above consideration the benefit risk balance for Nordimet for 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 is positive.

3.8. Conclusions

The overall B/R of Nordimet is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the new indication "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" for Nordimet; as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.3 has been adopted. The MAH took the opportunity to update the RMP with changes related to GVP V version 2 template and the outcome of MTX referral.
The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Nordimet-H-C-003983-II-0016

Attachments

1. Product information with changes highlighted as adopted by the CHMP on 10 December 2020