14 September 2023
EMA/439575/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Nordimet

International non-proprietary name: methotrexate

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

## Note

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

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# 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 4 November 2022 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 treatment of moderate to severe recalcitrant disabling psoriasis for NORDIMET, based on literature; As a consequence, sections 4.1 and 4.2 of the SmPC were updated. The Package leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted.

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

| Timetable | Actual dates |
|---|---|
| Submission date | 4 November 2022 |
| Start of procedure: | 26 November 2022 |
| CHMP Rapporteur Assessment Report | 7 February 2023 |
| PRAC Rapporteur Assessment Report | 27 January 2023 |
| PRAC Outcome | 9 February 2023 |
| CHMP members comments | 13 February 2023 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 19 February 2023 |
| Request for supplementary information (RSI) | 23 February 2023 |
| CHMP Rapporteur Assessment Report | 2 May 2023 |
| PRAC Rapporteur Assessment Report | 28 April 2023 |
| PRAC Outcome | 12 May 2023 |
| CHMP members comments | 15 May 2023 |
| Updated CHMP Rapporteur Assessment Report | 20 May 2023 |
| Request for supplementary information (RSI) | 25 May 2023 |
| CHMP Rapporteur Assessment Report | 2 August 2023 |
| PRAC Rapporteur Assessment Report | 18 August 2023 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | 29 August 2023 |
| PRAC Outcome | 31 August 2023 |
| CHMP members comments | 04 September 2023 |
| Updated CHMP Rapporteur Assessment Report | 7 September 2023 |
| Opinion | 14 September 2023 |

# 2. Scientific discussion

## *2.1. Introduction*

Methotrexate is available for clinical use and marketed since more than 15 years in most countries worldwide. Methotrexate 25 mg/ml solution for injection may be considered a hybrid medicinal product of the originator product Lantarel® FS 25 mg/ml from Pfizer (Germany).

This application is based on published scientific literature. No new pre-clinical tests or clinical trials were conducted for this application. Methotrexate solution of Lantarel (reference product) and the product submitted in this application are qualitatively and quantitatively comparable.

With this submission, the MAH proposes to add a new indication through variation number C.I.6.a: moderate to 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 currently approved indication is: 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.

Therefore, the extension of indication corresponds to the addition of moderate recalcitrant disabling psoriasis population.

### 2.1.1. Problem statement

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull-red scaly plaques, particularly on extensor parts of limbs and in the scalp.

The pathogenesis of psoriasis is still incompletely understood.

Psoriasis is a disabling disease and may even be life-threatening on rare occasions.

This is an extension of indication to include treatment of moderate plaque psoriasis in adults who are candidates for systemic therapy, based on literature.

### 2.1.2. About the product

Methotrexate is available for clinical use and marketed for more than 15 years in most countries worldwide. Methotrexate 25 mg/ml solution for injection, the product under consideration, is being considered a hybrid medicinal product of the originator product Lantarel® FS 25 mg/ml from Pfizer (Germany). The product under consideration will be supplied in prefilled pens containing volumes in a range of 0.3 ml to 1.0 ml. The document is prepared in accordance with the Notice to Applicants, Volume 2B, incorporating the Common Technical Document (May 2008).

Methotrexate is considered by many as first choice therapy among these slow-acting agents, also called disease modifying antirheumatic drugs (DMARD), for the treatment of rheumatoid arthritis [Visser et al (2009) in Albrecht et al (2010)]. (1)

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No SA has been sought. No new pre-clinical tests or clinical trials were conducted for this product.

### 2.1.4. General comments on compliance with GLP, GCP

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

## *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

An ERA was not submitted with this marketing authorization. The applicant considered that the absence of study data for ERA is justified. It is considered that the use of the proposed product would not lead to an increase in environmental exposure to methotrexate:

1. The requested indication for adults is already approved for another product in the EU (procedure: SE/H/0939).

2. The product is therefore intended as a substitute for other identical products already on the market. The approval of the proposed indication for Nordimet will not increase the total quantity of methotrexate released into the environment.

The Applicant considered that this ERA report is an addendum to the initial Environmental Risk Assessment (version 2016/06). Nevertheless, this extension of a new indication includes the inclusion of a new patient population, and according to question 2 of "Questions and answers document on the *Guideline on the environmental risk assessment of medicinal products for human use"* EMA/CHMP/SWP/44609/2010 Rev.1. 26 May 2016 an increase in environmental exposure is expected since the patient population is increased.

As a result, an updated Environmental Risk Assessment Report was presented by the MAH upon CHMP request. The sum of PEC surface water values for all therapeutic indications was calculated using the maximum prescribed dose. The PECsurfacewater value calculated is considered acceptable, in line with the Questions and answers document of the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* EMA/CHMP/SWP/44609/2010 Rev. 1, 2016.

The final PECsurfacewater does not exceed the action limit of 0.01 µg/L and experimental Log Kow of methotrexate is -1.855, far below the trigger value of 4.5. Therefore, a Phase II environmental fate and effect analysis is not considered necessary.

### 2.2.2. Discussion on non-clinical aspects

The ERA report is considered acceptable. As a result of the above considerations, Nordimet is unlikely to represent a risk to the environment following its prescribed usage in patients.

### 2.2.1. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of methotrexate. Considering the above data, methotrexate is not expected to pose a risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

No new pre-clinical tests or clinical trials were conducted for this product. New studies are not required as the methotrexate solution of Lantarel and the product under consideration are qualitatively and quantitatively comparable. This application is based on published scientific literature.

## GCP

There were no new clinical studies to support the updated indication.

## 2.3.2. Pharmacokinetics

This application is based on literature data. The below information summarises all available information based on literature data.

### *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.

Similarity with products from literature

The following characteristics of the medicinal product applied for in this procedure are comparable with the characteristics of the products used in the literature references and with approved products:

- Administration route

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 Crohn's disease consensus guidelines.

- Type of solution

*Table 1*

*A summary table of the type of solution, dosage and concentration of the products used in the pivotal studies demonstrating the efficacy of methotrexate 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.

- Concentration and dosage

The concentration of the products used in the pivotal studies by Feagan et al (1995) (2), Feagan et al (2000) (3) was not included in the references. Also, for the pivotal study by Feagan et al (2014) (4), the concentration of the products used was not included.

Therefore, it can be concluded that the concentration of the products used in the pivotal studies is the same as the concentration of the product submitted in this application.

- 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). (2) (3) (4)

*Table 2*

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

| 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.

After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m2 to 80 mg/m2 BSA), methotrexate has a mean bioavailability of approximately 70%, although considerable inter- and intra-subject variations are possible (25-100%). Plasma peak concentrations are attained within 1-2 hours. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.

Although oral administration seems to show some lower bioavailability when compared to the parenteral administration, the bioavailability of methotrexate is 11% to 15% lower after oral administration than those of the intramuscular or subcutaneous administration, nevertheless, the mean absolute bioavailability is very similar. This suggests that the routes of low dose pulse methotrexate administration are interchangeable. After oral administration the drug is metabolized by intestinal bacteria. In the liver, methotrexate is converted to 7-hydroxy-methotrexate. Less than 10% of a dose of methotrexate is oxidised by hepatic aldehyde oxidase to 7-hydroxy-methotrexate. Methotrexate is excreted primarily as the unchanged drug by the kidneys through a combination of glomerular filtration and active tubular transport. At serum concentrations from 0.1-0.4 µmol/L, tubular secretion prevails. At methotrexate plasma concentrations of 0.6-1 µmol/L, renal clearance equals creatinine clearance.

## *Distribution*

Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys, and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the body fluids in minimal amounts; under high doses (300 mg/kg body weight),

concentrations between 4 and 7 µg/ml have been measured in the body fluids. Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites).

The volume of distribution of methotrexate is 0.87-1.43 L/kg, which corresponds to the intracellular distribution of the drug. In blood, 30-70% of methotrexate is bound to proteins, almost exclusively to albumin. Distribution of low doses of methotrexate in body generally occurs into extravascular tissue compartments such as the kidneys, liver, and synovia generally with a half-life of 1 hour. Decrease of albumin concentration in elderly have minimal or no effect on MTX binding. Methotrexate is water-soluble, and its distribution may vary due to different intracellular water volume. There are no clinical relevance differences described.

## *Elimination*

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

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced enterohepatic blood flow exists. Clearance of methotrexate may decrease after long-term administration. Methotrexate treatment of moderate to severe psoriasis vulgaris and severe psoriatic arthritis represents long-term treatment where dose should be reduced gradually to the lowest possible effective maintenance dose.

## *Dose proportionality and time dependencies*

Renal clearance of methotrexate and creatinine clearance decrease after long-term methotrexate administration, which can be attributed to an increase in plasma adenosine concentrations in extracellular fluid and its effect on adenosine receptors in kidneys. Thus, non-linear elimination may result following the administration of 7.5-30 mg of methotrexate and contribute to the inter-individual variability in methotrexate concentrations.

## *Special populations*

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

## *Pharmacokinetic interaction studies*

Because of their effects on the gastrointestinal mucosa, antineoplastics have the potential to interfere with the absorption of drugs given orally. Antineoplastics that have an immunosuppressant effect may reduce the response to vaccines, and there is a possibility of generalised infection with live vaccines. Use with live vaccines should generally be avoided. Many antineoplastics are inhibitors of certain isoenzymes of cytochrome P450 and some antineoplastics are also metabolised by these enzymes, and in consequence the possibility of interactions between antineoplastics, or between antineoplastics and other medication, cannot be discounted [Martindale (2020b]). (5)

The effects of methotrexate (MTX) may be enhanced by drugs that decrease its renal excretion, such as non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates, probenecid, and some penicillins. Fatal toxicity has occurred in patients given NSAIDs with methotrexate. Severe toxicity has occurred rarely

when cotrimoxazole or trimethoprim was given with methotrexate. Use with other myelotoxic, hepatotoxic, or nephrotoxic agents may increase the risk of toxicity. Folic acid and its derivatives may decrease the efficacy of methotrexate, although they are often used together to reduce methotrexate toxicity [Martindale (2020a)]. (6)

Animal studies suggested methotrexate toxicity may be increased by chloramphenicol, para-aminobenzoic acid, and hypoglycaemics, but there does not appear to be any evidence of this clinically [Martindale (2020a)]. (6)

The electronic Medicines Compendium-50 (2014) (7) lists interactions with alcohol, hepatotoxic (e.g. leflunomide, retinoids) or haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine), antibiotics, medicinal products with high plasma protein binding (salicylates, hypoglycaemics, diuretics, sulfonamides, diphenylhydantoins, tetracyclines, chloramphenicol and paminobenzoic acid), probenecid, weak organic acids, pyrazoles and NSAIDs, sulfonamides, trimethoprim-sulfamethoxazole, folic acid, sulfasalazine, mercaptopurine, proton-pump inhibitors (e.g. omeprazole, pantoprazole), theophylline and caffeine- or theophylline-containing beverages.

MTX interactions with NSAIDs raise some concern. These most frequently result in mild diminution in creatinine clearance and are extremely rare causes of clinical toxicity. No great difference exists between aspirin and other NSAIDs with respect to renal toxicity [Furst (1995), Rooney et al (1993), Furst (1990), Songsiridej et al (1990) in Furst (1997)] (8). Case reports of clinically important adverse events after NSAID use together with MTX include leukopenia after aspirin; gastrointestinal toxicity after azapropazone, indomethacin and naproxen; bone marrow hypoplasia or aplasia after diclofenac, ketoprofen and azapropazone; and renal failure after diclofenac, indomethacin and ketoprofen [Furst (1995) in Furst (1997)] (8). Also, according to Wallace et al (1993) [in Maryles et al (2003)] (9), some NSAID's increase circulating blood levels of methotrexate, thereby increasing the risk of bone marrow toxicity. This is of particular importance when treating older patients (who can be predicted to have relatively limited renal function) with arthritis. However, the newer data suggest that some anti-inflammatories, including sulfasalazine, ketoprofen and celecoxib, have no known interactions with methotrexate and are therefore preferred in combination therapy [Tracy et al (1994), Karim et al (1999), O'Dell et al (2002) in Maryles et al (2003)]. (9)

There have been at least seven documented cases of pancytopenia or other bone marrow suppression after the combined use of MTX and trimethoprim-sulfamethoxazole or trimethoprim [Furst (1995) in Furst (1997)]. (8) The mechanism of this rare interaction is not well understood.

Likewise, a potential interaction between MTX and corticosteroids indicates that patients on long-term corticosteroids may have as much as a 20% decrease in MTX clearance, accompanied by a 24% decrease in renal clearance [Lafforgue et al (1993) in Furst (1997)] (8). This potentially interesting interaction has been documented in a study of somewhat unconventional design and will need corroboration. While the addition of hydroxychloroquine to MTX results in fewer aspartate aminotransferase elevations in an observational study, this has not yet been corroborated in a prospective controlled study and it is also not clear that decreasing the frequency or degree of AST elevations is protective against cirrhosis [Fries et al (1990) in Furst (1997)] (8). A positive interaction between folic acid and MTX shows that the addition of 1 mg/day folic acid decreases MTX-induced toxicity, particularly with respect to stomatitis, and gastrointestinal side-effects [Fries et al (1990), Morgan et al (1985), Morgan et al (2004) in Furst (1997)] (8).

## 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 is intracellularly converted into methotrexate polyglutamates. Methotrexate polyglutamates are inhibitors of phosphoribosylamino-imidazolecarboxoamide (AICAR) transformylase. By inhibition of AICAR transformylase there is intracellular accumulation of AICAR, which is associated with increased intracellular adenosine release [Niehues et al (2006)] (10). Adenosine acts via specific membrane receptors present on neutrophils, lymphocytes, monocytes/macrophages, and endothelial cells. Adenosine is primarily responsible for the anti-inflammatory effect of low-dose therapy, while the antiproliferative effect (with high-dose methotrexate for the treatment of tumors) is mediated via inhibitors of dihydrofolate reductase and interference with DNA [Dolezalova et al (2005) in Niehues et al (2006)] (10). A study has shown that methotrexate 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)] (10).

MTX and MTX-polyglutamate inhibit the enzymes DHFR and thymidylate synthase, as well as other enzymes involved in de novo purine synthesis. In this way, they deplete the intracellular reserve of fully reduced folates, and thus affect transmethylation reactions. Other immunosuppressant effects of the drug include the inhibition of T and B lymphocytes, suppression of proinflammatory cytokines, and inhibition of chemotaxis of neutrophils and monocytes. In addition, MTX decreases DNA synthesis and induces apoptosis in keratinocytes [Ranganathan and Mcleod (2006) and Saporito and Menter (2004) in Dogra and Mahajan (2013)] (11). Because the pathogenesis of psoriasis involves an aberrant T-cell response, the immune system is a possible target for the antipsoriatic effects of MTX [Jeffes et al (1995) in Dogra and Mahajan (2013)] (11). MTX interferes with epidermal-cell kinetics, presumably through a temporary reduction in DNA synthesis [Heenen et al (1998) in Dogra and Mahajan (2013)] (11). It impairs complement C5a-induced skin response and leukotriene B4-induced intraepidermal penetration of granulocytes [Cronstein et al (1993) in Dogra and Mahajan (2013)] (11). Meephansan et al. [(2011) in Dogra and Mahajan (2013)] (11) reported that MTX significantly reduces serum levels of interleukin-22, a cytokine that promotes keratinocyte proliferation and dermal inflammation in psoriasis. Another mechanism of action is through reduction in the mRNA levels of peroxisome proliferator- activated receptor b/δ, a member of the nuclear hormone receptor superfamily that contributes to psoriasis pathogenesis [El Eishi et al (2011) in Dogra and Mahajan (2013)L] (11). Owing to the inhibition of 5-aminoimidazole-4 carboxamide ribonucleoside (AICAR) transformylase, MTX induces the release of adenosine, which inhibits generation of oxygen free radicals by polymorphonuclear cells (PMNs), adhesion of PMNs, macrophage-induced modulation of tumour necrosis factor-a, and proliferation of lymphocytes, explaining the anti-inflammatory and immune modulatory effects of MTX [Cronstein (2010) in Dogra and Mahajan (2013)] (11). Caffeine, a poorly selective adenosine receptor antagonist, blocks the anti-inflammatory effects of adenosine in vitro, and thus might interfere with the therapeutic actions of MTX [Silke et al (2001) and Nesher et al (2003) in Dogra and Mahajan (2013)] (11). Adenosine may be responsible for some of the AEs associated with MTX, including hepatotoxicity, fatigue and somnolence; these may result from its action on A1 and A2B receptors, which stimulates hepatic steatosis [Penz et al (2009) in Dogra and Mahajan (2013)] (11), and its action on A2A receptors plays a role in the development of hepatic fibrosis.

### *Primary and secondary pharmacology*

Given the proposal to include the moderate recalcitrant disabling psoriasis population in the therapeutic indication, it is relevant, from a pharmacodynamic point of view, to understand the differences in the severity classification.

According to an expert consensus, the definition of moderate-to-severe disease was '(PASI > 10 or body surface area [BSA] > 10) AND DLQI > 10', and for mild psoriasis 'PASI ≤ 10 AND BSA ≤ 10 AND DLQI ≤ 10'.

The International Psoriasis Council (IPC) ran a modified Delphi consensus process among its counsellors to categorize psoriasis severity and to redefine access criteria to systemic therapy. The most preferred statement from the IPC survey 'rejects the mild, moderate and severe categories in favour of a dichotomous definition: Psoriasis patients should be classified as either candidates for topical therapy or candidates for systemic therapy; the latter are patients who meet at least one of the following criteria: (a) body surface area >10%, (b) disease involving special areas and (c) failure of topical therapy'.

The severity definition that reached the second highest approval rate did provide a dichotomous distinction: '(a) mild or mild-to-moderate: that which can be adequately controlled with topical therapy alone; (b) moderate-to-severe or severe: that which requires phototherapy or systemic therapy (including biologics).'

A definition using precise numbers got only moderate support from the IPC counsellors, defining mild as BSA 0–5% with special areas not affected and with DLQI < 5, defining moderate as BSA 5–10% or special areas affected; or BSA 1–5% and DLQI 5–10, and defining severe as >10% BSA or special areas affected; or BSA 5%-10% and DLQI > 10.

The majority of available data with methotrexate provided by the MAH is referred to moderate-to-severe psoriasis or to severe psoriasis. Clinical guidelines often do not differentiate moderate from severe psoriasis and from a Clinical Pharmacodynamic point of view there is a lack of reliable PD endpoints/biomarkers to evaluate the difference of the methotrexate effect in these types of severity.

According to scientific and clinical guidelines, the most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI). Health-related quality of life (HRQoL) is an important aspect of psoriasis, not only in defining disease severity but also as an outcome measure in clinical trials. The Dermatology Life Quality Index (DLQI) is the most commonly used score for assessing the impact of psoriasis on HRQoL.

Criteria to further 'upgrade' mild disease to moderate-to-severe were defined as major involvement of visible areas, major involvement of the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques.

## 2.3.4. PK/PD modelling

The PK/PD relationship of methotrexate has been extensively characterized and from a pharmacodynamic point of view, given the variation proposed and maintenance of dose for the new population included in the indication, an alteration of this PK/PD relationship is not foreseen.

## 2.3.5. Discussion on clinical pharmacology

**Pharmacokinetics**

The clinical pharmacology of methotrexate is well described due to its extensive and long use. In the present application, the MAH was able to sufficiently substantiate that there is similarity between the product from the MAH and the ones described in the supportive literature showing efficacy and safety in patients with moderate to severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, psoralens and ultraviolet A (PUVA), and retinoids.

The applicant provided evidence of similarity in their product to several others used in clinical trials described in the literature for Crohn's disease. The applicant also provided a list of studies in the current indication where IV/IM/SC administrations were used. Although, again, no reference to specific formulations were made, taking in consideration that most resulted in similar conclusions independent of the route of administration (that also included oral), there is a strong rational for considering the current formulation equivalent to the ones used in the reported clinical trials.

The multiple DDI described for MTX are present in the SmPC.

**Pharmacodynamics**

With this submission, the MAH proposes to add a new indication moderate to 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.

In a general and non-specific way, the studies provided support for the use of methotrexate in the new patient populationcovered by this extension of indication. The MAH was asked to clarify the difference in magnitude of PASI reduction in moderate vs severe recalcitrant disabling psoriasis population. A comprehensive literature review was submitted by the MAH organising the findings in terms of PASI characterization of severity. The MAH has further reviewed the literature in order to scientifically support the interpretation of the correlation of PASI with disease severity and has also clarified the difference in magnitude of PASI reduction in moderate *vs* severe recalcitrant disabling psoriasis population.

## 2.3.6. Conclusions on clinical pharmacology

The applicant has provided sufficient data and clarifications to support the proposed extension of indication.

# *2.4. Clinical efficacy*

## 2.4.1. Dose response study

No dose-response study has been presented for this type II variation.

## 2.4.2. Main studies

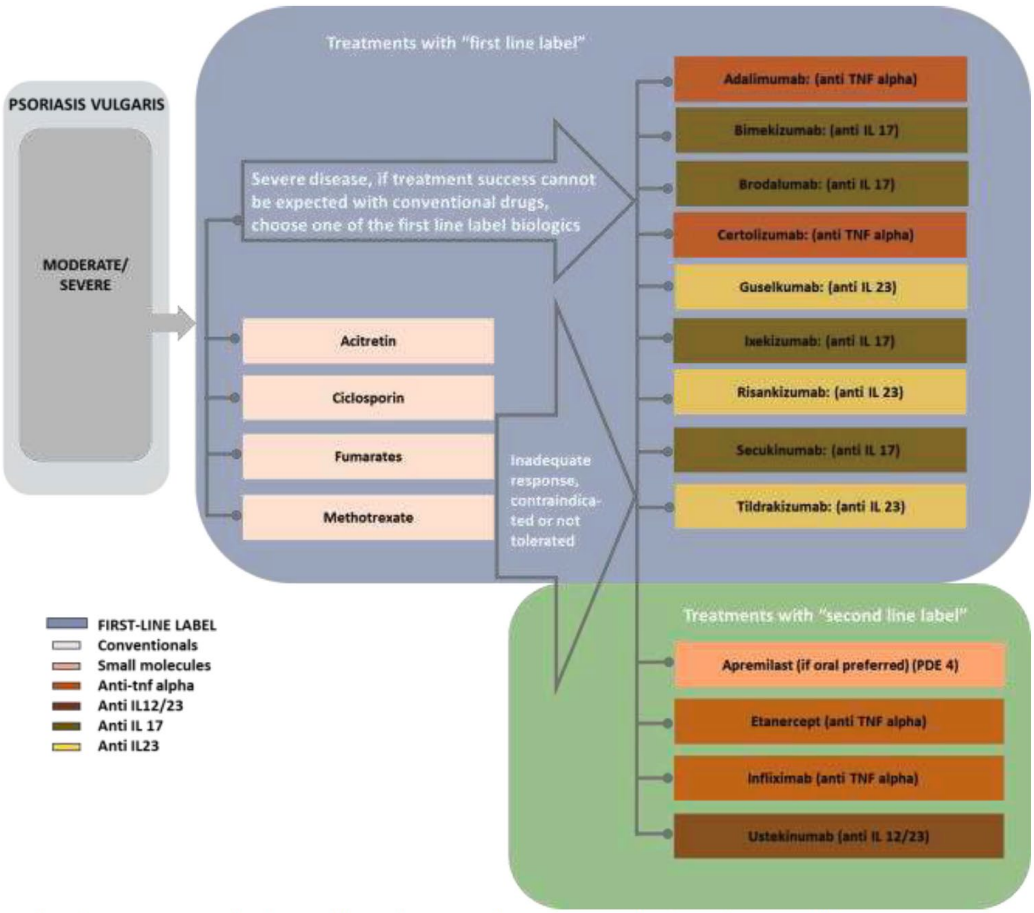
No new study has been presented for this type II variation. A review of relevant clinical data literature is presented below supporting the application for extension of indication.

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

Psoriasis is an inflammatory disease of the skin associated with increased epidermal proliferation. The aetiology of the disease is unknown, but there seems to be a genetic predisposition. The goal of therapy in the treatment of psoriasis is to decrease the rate of epidermal proliferation and the underlying inflammation [Tung et al (1990)] (12).

The Eurogioderm guideline for the systemic treatment of psoriasis suggests methotrexate as preferred first-line therapy in patients with psoriasis and ischemic heart disease if other patient characteristics do not preclude its use [Nast et al. (2022)] (13). It also suggests that methotrexate, acitretin and apremilast should be considered as treatment in patients with psoriasis and advanced congestive heart failure. The guideline does not recommend the use of methotrexate in moderate to severe psoriasis for patients that also have diabetes mellitus or metabolic syndrome or are pregnant or trying to become pregnant [Nast et al. (2022)] (13).

*Table 3 Overview of main recommendations (flow chart) and recommendations for specific treatment circumstances (decision grid I+II) [Nast et al. (2020)].*




*Overview of main recommendations (flow chart) and recommendations for specific treatment circumstances (decision grid I +II) [**Nast et al.** (2022)].*

Placebo-controlled trials designed to test the efficacy of methotrexate for psoriatic arthritis were carried out since 1964 [Black et al (1964) in Warren et al (2008)] (14). In addition to improvement of arthritis,

a significant improvement in psoriasis was observed. Efficacy was assessed using different doses and dosing regimens that are used nowadays.

Although the literature is sparse, there are several more recent studies demonstrating methotrexate efficacy for psoriasis. More recently, methotrexate has been compared directly with cyclosporine therapy in a randomized controlled trial for the treatment of moderate to severe psoriasis. At 16 weeks of treatment, there was no significant advantage of one drug over the other with a psoriasis area severity index (PASI) 75 of 60% and 71 % for methotrexate and cyclosporine, respectively. However, 28% of patients randomized for methotrexate dropped out of the study because of elevated liver enzyme levels vs 2% (elevated bilirubin) in the cyclosporine group [Heydendael et al (2003) in Warren et al (2008)] (14). There have been differing experiences in success rates of treating pustular variants of psoriasis, some claiming a higher success rate in these subgroups and others lower [Collins et al (1992), Baker (1976) in Warren et al (2008)] (14).

A 26-year retrospective study evaluated 150 severe psoriatics chronically treated with weekly low-dose methotrexate. Although 76% reported "good" success with methotrexate, 61% experienced side effects, including abnormal liver function tests, bone marrow toxicity, nausea and other gastrointestinal symptoms, and hair loss [Haustein et al (2000) in Maryles et al (2003)] (9).

Methotrexate is an effective treatment for psoriatic arthritis at doses similar to those used for psoriasis, with lower doses being possible in the maintenance phase of therapy [Zachariae et al (1987) in Warren et al (2008)] (14). In addition, methotrexate can significantly improve psoriatic nail dystrophy in a proportion of patients [Nyfors (1978) in Warren et al (2008)] (14).

In the study by Heydendael with 88 patients (grade of evidence A2), monotherapy with methotrexate was compared to monotherapy with cyclosporine. Using a PASI reduction of 90% as an outcome measure, the study showed that a higher percentage of patients treated with methotrexate achieved total remission (40%) compared to those taking cyclosporine (33%). For a PASI reduction of 75%, however, cyclosporine demonstrated higher efficacy, with 71% of patients achieving partial remission compared to 60% of patients taking methotrexate [Heyendael et al (2003) in JEADV (2009)] (15).

Of 11 studies investigating the efficacy of methotrexate monotherapy in psoriasis vulgaris, a total of three fulfilled the criteria for inclusion in the guidelines. After 16 weeks of treatment with methotrexate, approximately 60% of patients displayed a 75% reduction in PASI (level of evidence 2) [JEADV (2009)] (15).Clinical experience with methotrexate is much greater than the documentation of the efficacy and safety of methotrexate therapy in clinical studies. Clinical experience has demonstrated that the efficacy of methotrexate continues to increase with longer treatment. As a result, methotrexate represents, above all, an effective therapeutic option for long-term therapy. Its clinical application is restricted by severe adverse drug reactions, including especially hepatotoxicity, bone marrow suppression, gastrointestinal ulcerations, and very rare, but severe idiosyncratic reactions. However, with precise patient selection, thorough patient information, strict monitoring, use of the lowest effective dose, and the additional administration of folic acid, an acceptable safety profile can also be attained for methotrexate therapy [JEADV (2009)] (15).

Since the publication of the European S3-Guidelines on the systemic treatment of psoriasis vulgaris in 2009, further clinical trials in moderate-to-severe psoriasis have been conducted and the Eurogioderm guideline for the systemic treatment of psoriasis [Nast et al. (2022)] (13) has provided recommendation on the use of methotrexate in moderate-to-severe psoriasis. Table 2 shows the various clinical studies in which MTX has been used as monotherapy in moderate to severe psoriasis [Haustein and Rutter (2000), Heydendael et al. (2003), Ranjan et al. (2007), Flytström et al. (2008), Saurat et al. (2008), Akhyani et al. (2010), Reich et al. (2010), Ho et al. (2010), Fallah Arani et al. (2011), Barker et al. (2011), Reich et al. (2011), Kumar et al (2002), Sandhu et al (2003), Schewash-Millet and Ziprkowski

(1968), Baker (1970), Collins and Rogers (1992), van Dooren-Greebe et al (1994) and van Dooren-Greebe et al (1995) in Dogra and Mahajan (2013)] (11). The response to monotherapy is usually seen in 1–4 weeks, with at least 50% reduction in PASI in 70–80% of treated patients. MTX has also been combined with several other systemic or topical agents to decrease its total cumulative dose and hence its side-effects, and also to increase the efficacy of the treatment [Dogra and Mahajan (2013)]. (11)

*Table 4 Efficacy of methotrexate (MTX) as monotherapy in moderate to severe psoriasis [**Dogra and Mahajan** (2013)] (11)*

| References | Study design | Patients, n | Dose of MTX | Results |
|---|---|---|---|---|
| Schewach et al.[77] | Open-label prospective study | 17 | Intramuscular 12.5–37.5 mg/week | Maximum response in 3 patients, good to moderate in 11 and minimal in 3 |
| Baker et al.[78] | Open-label prospective study | 18 | 25 mg/week | Clinical response was highly satisfactory in 11 (63%) and worthwhile[a] in 5 others |
| Weinstein et al.[27] | Open-label study | 26 | 7.5 mg/week | 20/26 patients attained 75–100% improvement |
| Collins et al.[79] | Retrospective study over 10 years | 40 | Initially 15 mg/week followed by 12.5 mg/week | MTX was particularly effective in controlling erythrodermic and generalized pustular psoriasis |
| van Dooren-Greebe et al.[80] | Retrospective study over 22 years | 113 | 15 mg/week | 81% of the patients had near clearance |
| van Dooren-Greebe et al.[81] | Study of the effects of intermittent treatment on long-term treatment with low-dose oral MTX | 10 | 15 mg/week | Interruption of long-term MTX treatment led to a substantial reduction in cumulative MTX dose |
| Haaustein et al.[82] | Retrospective study over 26 years | 157 | < 15–20 mg/week | Good response seen in 76% of patients, moderate response in 18% and poor response in 6% |
| Kumar et al.[32] | Retrospective study over 20 years | 244 | 0.3–0.5 mg/kg/week | PASI 75 achieved in 88% of patients in 8.5 ± 5.1 weeks |
| Hyedendial 83 | Comparison of efficacy and safety of weekly MTX with daily ciclosporin | 88 | 15 mg/week (ciclosporin was 3 mg/kg/day) | No significant difference between the two therapies |
| Sandhu et al.[33] | Comparison of efficacy and safety of weekly MTX with daily ciclosporin | 30 | 0.5 mg/kg/week (ciclosporin was 3 mg/kg/day; increased to a maximum of 4 mg/kg/day) | PASI 75 achieved in 5.3 weeks with MTX and 6.8 weeks with ciclosporin |
| Ranjan et al.[84] | Open-label study to compare efficacy of hydroxyurea with MTX | 30 | 15–20 mg/week | Weekly doses of hydroxyurea can be an alternative to MTX |
| Flytstorm et al.[85] | RCT to compare efficacy of MTX with ciclosporin | 68 | 15 mg/kg/week maximum (ciclosporin 3 mg/kg/day, increased to a maximum of 5 mg/kg/day) | Mean PASI change from baseline at 12 weeks was 58% in the MTX group and 72% in the ciclosporin group |
| Saurat et al. (CHAMPION trial)[86] | Noninferiority RCT | 271 | 7.5–25 mg/week | PASI 75 achieved by 80% of patients in adalimumab group, 36% in the MTX group and 19% in the placebo group |
| Akhyani et al.[87] | Open-label trial of MMF vs. MTX | 18 | 7.5–25 mg/week | No significant differences in efficacy between the MTX and MMF groups |
| Reich et al.[88] | Noninferiority RCT of adalimumab with MTX and placebo | 270 | 7.5–25 mg/week | With four times as many AE-free response days, adalimumab demonstrated a superior risk–benefit profile |
| Ho et al.[89] | RCT to compare MTX with TCM | 61 | 15 mg/week | MTX significantly better than TCM |
| Fallah et al.[90] | RCT to compare MTX with fumarates | 60 | 15 mg/week | No significant differences in efficacy between MTX and fumaric acid groups |
| Barker et al.[91] | Open-label RCT to compare infliximab with MTX | 868 | 15–20 mg/week | Infliximab significantly better than MTX |
| Radmanesh et al.[36] | RCT to compare MTX daily vs weekly dose | 202 | 2.5 mg/day for 6 days/week or 15 mg/week | Significantly better efficacy with weekly MTX, with fewer side-effects |
| Reich et al.[92] | RCT to compare MTX with briakinumab | 317 | 5–25 mg/week | Briakinumab significantly better than MTX |

AE, adverse effects; MMF, mycophenolate mofetil; PASI, Psoriasis Area and Severity Index; RCT, randomized controlled trial; TCM, traditional Chinese medicine.

[a] The authors used subjective and objective measures, including abolition of itching, reduction in scaling and clearance of lesions.

Appani et al (2019) (16) performed an open-label, prospective study of patients satisfying the ClASsification criteria for Psoriatic ARthritis study (CASPAR) criteria for psoriatic arthritis (PsA) who received MTX in doses of ≥15 mg/week throughout the follow-up period of 9 months. Disease activity was assessed across various domains by tender and swollen joint count, physician and patient global assessment, DAS-28 ESR, Clinical Disease Activity Index for PsA (cDAPSA), Leeds Dactylitis Instrument basic, Leeds Enthesitis Index (LEI), Psoriasis Area and Severity Index (PASI), Minimal Disease Activity and HAQ (CRD Pune version) at baseline and at 3, 6 and 9 months of follow-up. Response to therapy was assessed by EULAR DAS-28 ESR, cDAPSA response, HAQ response and PASI75. MTX dose escalation and the use of combination DMARDS were dictated by disease activity.

A total of 73 patients were included, with mean (SD) age 44 (9.7) years and a mean (SD) PASI score of 4.58 (6.19) at baseline. The mean (SD) dose of MTX used was 17.5 (3.8) mg/week. Seven patients received additional DMARDS (LEF/SSZa). At the end of 9 months, significant improvement (P< 0.05) was noted in the tender joint count, swollen joint count, global activity, DAS-28 ESR, cDAPSA, Leeds Dactylitis Index basic, LEI, PASI and HAQ. Major cDAPSA response was achieved in 58.9% of patients. EULAR DAS-28 moderate and good response was achieved in 74% and 6.8% of patients, respectively. Minimal disease activity was achieved in 63% of patients. A PASI75 response and HAQ response was achieved in 67.9% and 65.8% of patients, respectively [Appani et al. (2019)]. (16)

*Table 5 Response assessment at baseline and follow-up visits [Appani et al. (2019)] (16)*

| Response assessment | | Number of patients *n*: 73 (%) | | |
|---|---|---|---|---|
| | | 0–3 months | 0–6 months | 0–9 months |
| cDAPSA response | No response | 30 (41.1%) | 10 (13.7%) | 8 (11.0%) |
| | Minor response | 24 (32.9%) | 18 (24.7%) | 15 (20.5%) |
| | Moderate response | 6 (8.2%) | 13 (17.8%) | 7 (9.6%) |
| | Major response | 13 (17.8%) | 32 (43.8%) | 43 (58.9%) |
| EULAR DAS28 ESR response | No response | 30 (41.1%) | 12 (16.4%) | 14 (19.2%) |
| | Moderate response | 41 (56.2%) | 57 (78.1%) | 54 (74.0%) |
| | Good response | 2 (2.7%) | 4 (5.5%) | 5 (6.8%) |
| HAQ response | Yes | 38 (52.1%) | 46 (63.0%) | 48 (65.8%) |
| | No | 35 (47.9%) | 27 (37.0%) | 25 (34.2%) |
| PASI75 response | Yes | 20/53 (37.7%) | 34/53 (64.2%) | 36/53 (67.9%) |
| | No | 33/53 (62.3%) | 19/53 (35.8%) | 17/53 (32.1%) |

cDAPSA: Clinical Disease Activity Index for PsA, DAS28: DAS using 28 joint counts; PASI: Psoriasis Area and Severity Index.

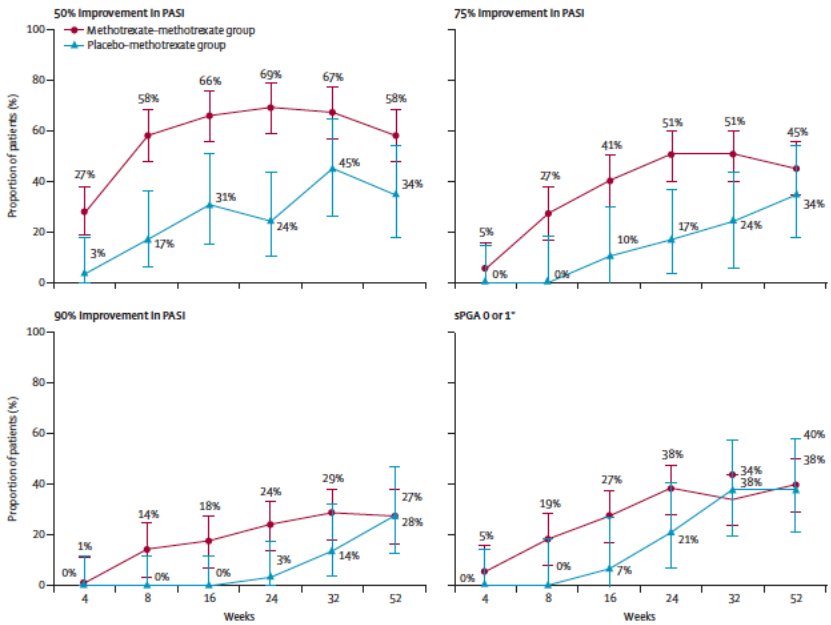
A prospective cohort involving consecutive at in 25 centres belonging to GEM RESOPSO group included all adults with plaque psoriasis in whom MTX treatment was performed by Tournier et al (2019) (17). The efficacy criterion was achievement of PASI 75 at week (W) 12/16. The impact of demographic data, psoriasis characteristics (duration, topography, rheumatism), dosage (W12/16 dosage, cumulative dose after 4 weeks), and mode of administration (subcutaneous vs. oral, concomitant use of folic acid) on efficacy was evaluated. Intention-to-treat (ITT), per protocol (PP), and multivariate analyses were performed.

Two hundred and fifty-six patients (F/M: 105/151; mean age: 45.0 years; rheumatism: 12.6%) with plaque psoriasis (PASI score of 13.1 ± 7.8 at baseline) were included. 99 patients were not analysed at W12/16 (16 because of inefficacy, 16 because of intolerance, 56 were lost to follow-up or had data missing). PASI 75 was achieved in 98 patients, with efficacy of 38.3% in the intention to treat (ITT) analysis and 58.3% in the PP analysis. In the ITT analysis, absence of previous use of cyclosporine (P = 0.01) and a cumulative dose of MTX > 60 mg after 4 weeks (P< 0.0001) were associated with higher PASI 75 rates. In the PP analysis, only absence of previous use of cyclosporine (P = 0.0009) was associated with a better PASI 75 results. There was no association between PASI 75 and patient characteristics (including body mass index), clinical aspects of psoriasis, route of administration,

combination with folic acid, or W12/16 dose. Adverse events were reported by 34.8% of patients. These consisted mainly of digestive disorders (nausea, abdominal pain), asthenia and moderate hepatic cytolysis. The frequency of adverse events was correlated with methotrexate dosage. The authors concluded that their results were consistent with the data in the literature [Tournier et al. (2019)]. (17)

Warren et al (2017) (18) performed a prospective, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (METOP) at 16 sites in Germany, France, the Netherlands, and the United Kingdom. Eligible patients were aged 18 years or older, had a diagnosis of chronic plaque psoriasis for at least 6 months before baseline, had currently moderate to severe disease (mean (SD) PASI score at baseline 15.4 (5.9)), and were methotrexate treatment naive. Participants were randomly assigned (3:1), via a computer-generated random number sequence integrated into an electronic data capture system, to receive either methotrexate at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by methotrexate treatment of all patients up to 52 weeks (methotrexate–methotrexate vs placebo–methotrexate groups). Dose escalation to 22.5 mg/week was allowed after 8 weeks of methotrexate treatment if patients had not achieved at least a 50% reduction in baseline PASI score, with corresponding volume increases in placebo injections. Treatment was combined with folic acid 5 mg/week. Group allocation was concealed from participants and investigators from the time of randomisation until an interim database lock at week 16, and was open label from week 16 onwards, with no masking of participants or investigators. The primary efficacy endpoint was a 75% reduction in PASI score (PASI 75) from baseline to week 16. Between Feb 22, 2013, and May 13, 2015, 120 patients were randomly assigned to receive methotrexate (n=91) or placebo (n=29). At week 16, a PASI 75 response was achieved in 37 (41%) patients in the methotrexate group compared with three (10%) patients in the placebo group (relative risk 3.93, 95% CI 1.31–11.81; p=0.0026). Subcutaneous methotrexate was generally well tolerated; no patients died or had serious infections, malignancies, or major adverse cardiovascular events. Serious adverse events were recorded in three (3%) patients who received methotrexate for the full 52-week treatment period. The authors remark that their findings show a favourable 52-week risk–benefit profile of subcutaneous methotrexate in patients with psoriasis [Warren et al. (2017)]. (18)

Data shown in the figure below are based on modified intention-to-treat non-responder imputation analysis. Error bars represent exact 95% CIs. Patients received methotrexate (n=91) or placebo (n=29) up to week 16, followed by methotrexate treatment of all patients up to week 52.



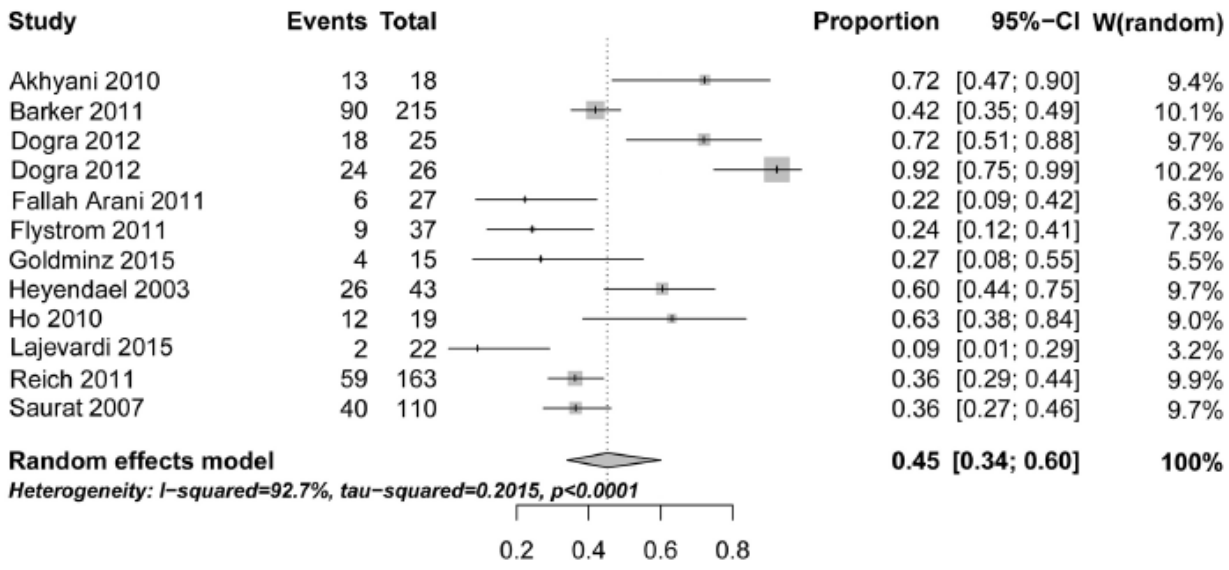
*Proportion of patients achieving reductions of 50%, 75%, and 90% in PASI score and an sPGA score of 0 or 1 over the 52 week treatment period [Warren et al. (2017)] PASI=Psoriasis Area and Severity Index. sPGA=static Physicians' Global Assessment. *An sPGA of 0 indicates clear of disease and an sPGA of 1 indicates almost clear of disease.*

Noor et al (2017) compared the treatment efficacy and safety of methotrexate with acitretin in chronic plaque psoriasis. A total of 142 patients were enrolled, 71 patients in each group. Patients were randomly divided into two groups, A and B by lottery method. They were given methotrexate (25 mg injection deep I/M once weekly) or acitretin (0.4mg/kg orally daily). At the end of 24 weeks, response to treatment was evaluated in terms of reduction in PASI score. Safety of treatment was accessed in terms of laboratory investigations i.e., transaminase, triglycerides, platelets and white blood cells during treatment. In the methotrexate group, an excellent response (PASI-75%) was noted in 38 (53.5%), good response (PASI-50%) in 13 (18.3%), fair response (less than 50% reduction in PASI) in 4 (5.6%), and no response was observed in 1 (1.4%) patient. In acitretin treated group excellent response was noted in 18 (25.3%), good response in 27 (38.0%), fair response in 8 (11.2%), and no response was observed in 5 (7.04%) of patients. The authors concluded that methotrexate is a better option for treatment of moderate to severe plaque psoriasis than acitretin [Noor et al. (2017)] (19).

West et al (2016) performed a meta-analysis on efficacy in psoriasis, according to PRISMA checklist. Eleven studies met the criteria for study design and passed a Cochrane risk of bias analysis. Based on this dataset, 45.2% [95% confidence interval 34.1-60.0] of patients achieve 75% reduction of PASI from baseline (PASI75) at primary endpoint (12 or 16 weeks, respectively, n = 705 patients across all studies), compared to a calculated PASI75 of 4.4 [3.5-5.6] for placebo, yielding a relative risk of 10.2 [95% C.I. 7.1-14.7]. The figure above graphically summarises the PASI75 reported in the MTX-only treatment arm at 12 or 16 weeks, respectively, in each of the studies analysed. As evident from the figure, there is notable heterogeneity between studies (I2 = 92.7%)

The pooled PASI75 estimate calculated across all studies yielded at PASI75 of 45.2% (95% confidence interval 34.1%– 60.0%) compared to a calculated PASI75 of 4.4% for placebo (95% confidence interval 3.5%– 5.6%) (Table 6). This yields a relative risk of 10.2 (95% confidence interval 7.1– 14.7). The authors conclude that across published MTX studies on psoriasis, approximately 40% of patients achieve PASI75 between weeks 12– 16.

*Table 6* ***Pooled PASI75 estimate***



Forest plot of efficacy (PASI75 outcome reported at 12 or 16 weeks) of MTX in psoriasis as reported in the published clinical studies analysed by West et al (2016) (20).

Von Drateln et al. (2015) (21) conducted a double-blind clinical trial comparing pioglitazone versus methotrexate in two groups of adult patients with psoriasis. Patients were scheduled every month for two months, the PASI (Psoriasis Area Severity Index) were assessed and complete blood count, blood chemistry and liver profile were taken every time. Statistical analysis was performed using Mann-Whitney U, Wilcoxon signed-rank test and $\chi 2$ test. A total of 9 patients were included, 4 in the pioglitazone group and 5 in the methotrexate group. The patients in the methotrexate group reduced their PASI score significantly after two months of treatment ($p = 0.03$), but not the pioglitazone group ($p = 0.3$) No adverse effects were reported in either group [Von Drateln et al. (2015)] (21).

Barker et al (2011) (22) compared the efficacy and safety of infliximab vs. methotrexate (MTX) in adults with moderate-to-severe plaque psoriasis. MTX-naïve patients (n = 868) were randomized 3 : 1 to receive infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 or MTX 15 mg weekly with a dose increase to 20 mg weekly at week 6 if the Psoriasis Area and Severity Index (PASI) response was < 25%. At week 16, patients with < PASI 50 response could switch treatment groups. The primary efficacy endpoint was PASI 75 response at week 16. Major secondary efficacy endpoints were PASI 75 response at week 26, and the proportion of patients achieving a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) at weeks 16 and 26. Others included Dermatology Life Quality Index, 36-Item Short Form Health Survey, and PGA, PASI 50, PASI 75 and PASI 90 responses over time. The primary endpoint was achieved by a significantly greater proportion of infliximab-treated patients (508 /653, 78%) than MTX-treated patients (90 /215, 42%; P < 0.001). Key secondary endpoints also were achieved by a greater proportion of infliximab-treated patients. Similar responses were observed at week 26 in patients who switched from MTX to infliximab at week 16. Overall adverse event (AE) incidence was comparable between groups, but incidence of serious and severe AEs was slightly higher in the infliximab group [Barker et al. (2011)] (22)

Fallah Arani et al (2011) conducted a randomized controlled trial comparing the effectiveness and the adverse events of methotrexate and fumarates. Sixty patients with moderate to severe psoriasis vulgaris were randomly assigned to treatment for 16 weeks with either methotrexate (30 patients, mean ± SD PASI score at baseline of 14.7±3.0; 15 mg per week) or fumarates (30 patients, mean ± SD PASI score at baseline of 18.0±6.9; 30 mg, followed by 120 mg according to a standard progressive dosage regimen) and were followed up for 4 weeks. The primary endpoint with respect to the efficacy was the difference in mean change from baseline in Psoriasis Area and Severity Index (PASI) after 12 weeks of treatment. The study was powered to detect a difference of five points. Analyses were by intention to treat. Six patients were excluded because five were not eligible and one withdrew consent. Two patients in the methotrexate group and one in the fumarate group dropped out during the 12 weeks of treatment because of non- appearance at the outpatient clinic. In total, 25 patients in the methotrexate group and 26 in the fumarate group were evaluated in the primary analysis. After 12 weeks of treatment, the mean ± SD PASI decreased from 14.5 ± 3.0 at baseline to 6.7 ± 4.5 in the 25 patients treated with methotrexate, whereas it decreased from 18.1 ± 7.0 to 10.5 ± 6.7 in the 26 patients treated with fumarates. After adjustment for baseline values, the absolute difference (fumarates minus methotrexate) in the mean values at 12 weeks was 1.4 (95% confidence interval) 2.0 to 4.7; P = 0.417) [Fallah Arani et al. (2011)] (23).

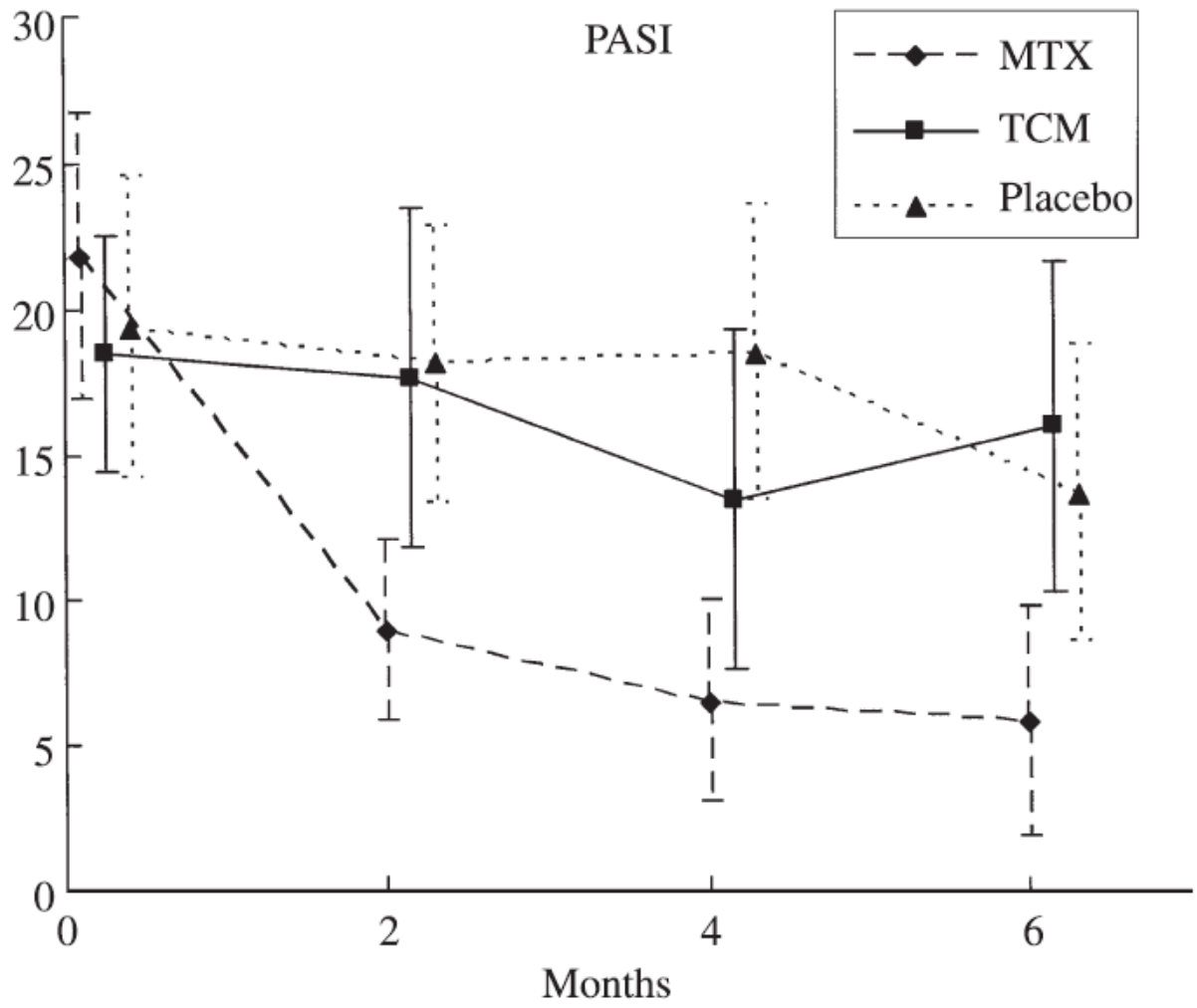
Reich et al. (2011) performed a 52-week clinical trial, in which 317 patients with moderate-to-severe psoriasis randomly assigned to briakinumab, at a dose of 200 mg at weeks 0 and 4 and 100 mg at week 8 and every 4 weeks thereafter (154 patients), or methotrexate at a dose of 5 to 25 mg weekly (163 patients). The primary end points were the percentages of patients with at least 75% improvement in the score on the psoriasis area-and-severity index (PASI) at weeks 24 and 52 and a score on the

physician's global assessment of 0 (clear; i.e., no apparent disease) or 1 (minimal disease) at weeks 24 and 52. A total of 248 patients were enrolled in an ongoing 160-week open-label continuation study. At baseline, the mean ± SD PASI score of the patients in the briakinumab group and methotrexate groups were 18.4±6.7 and 17.8±6.1, respectively. At week 24, a total of 81.8% of the patients in the briakinumab group versus 39.9% in the methotrexate group had at least 75% improvement in the PASI score, and 80.5% versus 34.4% had a score of 0 or 1 on the physician's global assessment. The corresponding percentages at week 52 were 66.2% versus 23.9% with at least a 75% improvement in the PASI score and 63.0% versus 20.2% with a score of 0 or 1 on the physician's global assessment (P<0.001 for all comparisons). During the 52-week study, serious adverse events occurred in 9.1% of the patients in the briakinumab group (12.9 events per 100 patient-years) and in 6.1% in the methotrexate group (10.6 events per 100 patient-years). Serious infections occurred in 2.6% of the patients in the briakinumab group (4.1 events per 100 patient-years) and in 1.8% in the methotrexate group (2.7 events per 100 patient-years); cancers occurred in 1.9% (2.0 events per 100 patient-years) versus 0% [Reich et al. (2011)] (24).

Akhyani et al. (2010) (25) compared the efficacy and safety of mycophenolate mofetil (MMF) vs. methotrexate (MTX) for the treatment of chronic plaque psoriasis. Thirty-eight consecutive patients with Psoriasis Area and Severity Index (PASI) >10 were randomly assigned for 12 weeks of treatment with either MTX (18 patients; initial dose, 7.5 mg/ week) or MMF (20 patients; dose; 2 g /day) and were followed for 12 weeks after discontinuing the treatment. The differences between the two groups were analysed at the end of treatment and follow-up comparing with baseline values. After 12 weeks of treatment, the mean ± SD score for the PASI decreased from 16.46 ± 5.29 at baseline to 3.17 ± 2.35 among 15 patients treated with MTX, whereas the score decreased from 17.43 ± 7.42 to 3.97 ± 5.95 among 17 patients treated with MMF (P >0.05). Twelve weeks after discontinuing the treatment, the scores were 4.77 ± 3.52 and 5.94 ± 4.27, respectively (P >0.05). PASI-75 were achieved in 58.8% of patients in MMF group and 73.3% in MTX group (P > 0.05). Three months after discontinuing the treatment, PASI-75 remained in 33.3% of patients in MMF and 53.3% of MTX group (P > 0.05). Both drugs were well tolerated, and side-effects were minor and transient [Akhyani et al. (2010)] (25).

Ho et al (2010) performed a randomized placebo-controlled trial comparing methotrexate, placebo, and traditional Chinese medicine (TCM) in terms of efficacy, safety, and quality of life for the treatment of psoriasis. In total, 61 patients with moderate to severe plaque psoriasis were randomized to receive treatment with methotrexate, TCM or placebo for 6 months. The primary outcome measure was the Psoriasis Area and Severity Index (PASI), and secondary outcome measures were the Physician's Global Assessment (PGA) and the Psoriasis Disability Index (PDI). In all, 50 patients completed the study and were included in the analysis. For the patients who completed the study, mean ± SD PASI at baseline was 22.0 ± 11.3 in the methotrexate group, 18.9 ± 8.2 in the TCM group and 20.4 ± 10.8 in the placebo group. Dropout rates were highest in the TCM group. For the patients who completed the study, mean ± SD PASI at baseline was 22.0 ± 11.3 in the methotrexate group, 18.9 ± 8.2 in the TCM group and 20.4 ± 10.8 in the placebo group. After 6 months of treatment, the scores were 5.7 ± 8.5, 16.0 ± 9.8 and 13.9 ± 10.1, an improvement of 73.9%, 15.1% and 32%, respectively. There was a significant difference between the three groups, with methotrexate showing greater effectiveness than the other two groups. No significant difference was found between the TCM and placebo groups. The methotrexate group also had greater improvement when assessed using the PGA and PDI. Adverse Events were reported by 65% of the MTX group, 48% of the TCM group and 30% of the placebo group. Nausea, vomiting and increased liver enzyme levels were common in the MTX group. The TCM group reported infections and gastrointestinal side-effects, and a few developed abnormalities in liver function. The placebo group also reported infections and had increased liver enzymes. [Ho et al. (2010)] (26).

*Table 7 PASI scores at 2, 4 and 6 months of treatment. Results are shown as mean ± 95% confidence interval [Ho et al. (2010)]. (26)*




Ranjan et al (2007) (27) performed a small comparative trial where two groups of 15 patients each, having moderate-to-severe chronic plaque psoriasis, were given weekly doses of methotrexate (15–20 mg/week) or hydroxycarbamide (3–4.5 g/week). The severity of psoriasis was defined by a score of >10 on the Psoriasis Area and Severity Index (PASI) scale and involvement of at least 20% of the body surface area. The clinical response was assessed by the percentage reduction in the baseline PASI scores for the next 12 weeks.

At the end of 12 weeks, the mean PASI score in the methotrexate group was 5.69±5.93 (baseline=25.11±11.75), while it was 11.44±6.63 (baseline=22.99±5.66) in the hydroxycarbamine group. The mean percentage reduction in the PASI score at 12 weeks was 77.28±18.80 in the methotrexate group and 48.47±26.53 in the hydroxycarbamine group. Ten (66.66%) patients in the methotrexate group achieved >75% reduction in the PASI score, while in the hydroxycarbamide group only two (13.33%) patients showed similar results, signifying that methotrexate leads to a faster clearance of the disease. The methotrexate-related side effects, however, were also higher [Ranjan et al. (2007)]. (27)

*Table 8 Baseline characteristics and psoriasis severity score [Ranjan et al. (2007)]. (27)*

| Characteristics | Group 1 Methotrexate group ($n$=15) | Group 2 Hydroxycarbamide group ($n$=15) |
|---|---|---|
| Sex (M:F) | 12:3 | 14:1 |
| Age (years) | | |
| Range | 18–72 | 25–60 |
| Mean | 44.93±15.42 | 40.67±11.37 |
| Duration of disease (years) | | |
| Range | 0.2–20 | 0.08–30 |
| Mean | 7.58±5.95 | 8.07±7.92 |
| Pretreatment PASI score | | |
| Range | 15.2–32.5 | 14.0–53.4 |
| Mean | 25.11±11.75 | 22.99±5.66 |
| Mean percentage reduction in PASI score at: | | |
| 4 weeks | 37.10±19.52 | 24.83±19.21 |
| 8 weeks | 57.90±19.68 | 36.26±25.13 |
| 12 weeks | 77.28±18.80 | 48.47±26.53 |

Psoriasis Area and Severity Index (PASI) score of >10 and involvement of at least 20% of the body surface area was considered to be moderate-to-severe disease. At the end of 12 weeks, 10 (66.66%) patients in the methotrexate group achieved >75% reduction in the PASI score, while in the hydroxycarbamide group only two (13.33%) patients showed similar results.

Heydendael et al (2003) conducted a randomized, controlled trial comparing methotrexate and cyclosporine in terms of effectiveness, side effects, and the quality of life. A total of 88 patients with moderate-to-severe psoriasis were randomly assigned to treatment for 16 weeks with either methotrexate (44 patients, PASI score; initial dose, 15 mg per week) or cyclosporine (44 patients; initial dose, 3 mg per kilogram of body weight per day) and were followed for another 36 weeks. The primary outcome was the difference between groups in the psoriasis area-and-severity index after 16 weeks of treatment, after adjustment for base-line values; scores were determined in a blinded fashion by trained observers.

Two patients were excluded from the analysis after randomization because they were found to be ineligible, and one patient withdrew his consent. Twelve patients in the methotrexate group had to discontinue treatment because of reversible elevations in liver-enzyme levels, and 1 patient in the cyclosporine group had to do so because of an elevation in the bilirubin level, but all 13 were included in the analysis. After 16 weeks of treatment, the mean (±SE) score for the psoriasis area-and-severity index decreased from 13.4±3.6 at base line to 5.0±0.7 among 43 patients treated with methotrexate, whereas the score decreased from 14.0±6.6 to 3.8±0.5 among 42 patients treated with cyclosporine. After adjustment for base-line values, the mean absolute difference in values at 16 weeks was 1.3 (95 percent confidence interval, −0.2 to 2.8; P=0.09). The physician's global assessment of the extent of psoriasis, the time to and the rates of remission, and the quality of life were similar in the two groups [Heydendael et al. (2003)] (28).

Cardiovascular comorbidity

Moderate-to-severe psoriasis is associated with several well-established cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidaemia, and metabolic syndrome [Boehncke et al (2011) in Nast et al. (2022)] (13). Psoriasis severity has been linked to a higher prevalence of these risk factors. However, there is conflicting evidence as to whether psoriasis is associated with increased cardiovascular events and whether psoriasis itself represents is an independent cardiovascular risk factor [Kimball et al (2012) Nast et al. (2022)] (13). A recent systematic review and meta-analysis indicates that subclinical coronary artery disease diagnosed with cardiac computed tomography angiography is more prevalent in patients with psoriasis, with an increased burden of disease and number of high-risk coronary plaques [Kaiser et al (2019) in Nast et al. (2022)]. (13)

Therapy with methotrexate is associated with a reduced risk of cardiovascular morbidity and mortality in patients with RA as well as in patients with psoriasis and psoriatic arthritis [Choi et al (2002), Prodanovich et al (2005), Westlake et al (2010) and Roubille et al (2015) in Nast et al. (2022)] (13). In a longitudinal cohort study of 6902 patients with psoriasis, Ahlehoff et al. found that treatment with methotrexate was associated with a reduced risk of cardiovascular events compared to patients treated with other antipsoriatic therapies such as ciclosporin and retinoids [Ahlehoff et al (2015) in Nast et al. (2022)] (13). Methotrexate therapy decreases carotid intima-media thickness (a marker of arteriosclerosis) in patients with moderate to severe psoriasis [Martinez-Lopez et al (2018) in Nast et al. (2022)] (13). Preclinical and pilot studies suggest possible cardioprotective effects of apremilast and fumarates but there is no clinical evidence that either affect cardiovascular risk [Schmieder et al (2015) and Imam et al (2018) in Nast et al. (2022)] (13).

In a retrospective study by Van Dooren-Greebe et al., [(1995) in Dogra and Mahajan (2013)] (11) 113 patients with severe psoriasis were treated with low-dose MTX over 22 years. The treatment resulted in prolonged clearance or near clearance in 81% of the patients, while 73% of the patients had side-effects, most frequently abnormal liver function tests, nausea and gastric symptoms. The maximum weekly dosage was 15 mg (Weinstein schedule), with the mean cumulative dose being 4.803g.

In another retrospective study, Kumar et al. [(2002) in Dogra and Mahajan (2013)] (11) reviewed the data on 244 patients with psoriasis who were given once-weekly oral MTX at the full therapeutic dose (0.3–0.5 mg/kg/week) during the period 1981–2000. An improvement of > 75% occurred in 88% of patients in 8.5 ± 5.1 weeks, and only three patients had significantly abnormal liver-function tests. Liver biopsies were taken before (34 biopsies) and after (13 biopsies) MTX therapy, which showed grade I/II changes that were nonprogressive. These studies confirm the effectiveness of MTX monotherapy in moderate to severe psoriasis.

Comparing MTX with other therapies such as ciclosporin has shown conflicting results. Sandhu et al. [(2003) in Dogra and Mahajan (2013)] (11) found MTX to provide a faster relief than ciclosporin, whereas Haydendael et al. [(2003) in Dogra and Mahajan (2013)] (11) did not find any significant difference between the two agents. In a randomized controlled study comparing both of these agents, ciclosporin was found to be significantly more effective than MTX in treating psoriasis [Flytström et al. (2008), in Dogra and Mahajan (2013)]. (11)

With the increasing use of biological response modifiers in psoriasis and PsA, there is a need for comparisons of these agents with MTX. The CHAMPION trial [Comparative Study of Humira (adalimumab) with Methotrexate with Placebo in Patients with Psoriasis]) [Saurat et al. (2008), in Dogra and Mahajan (2013)] (11) can be considered a landmark study, as it evaluated the efficacy and safety of MTX versus a biological drug. At the end of the 16-week treatment period, PASI75 was achieved by 80% patients in the adalimumab group, 36% patients in the MTX group and 19% patients in the placebo group, while PASI 100 was achieved by 17% patients receiving adalimumab, 7% patients receiving MTX and 2% patients receiving placebo. It was concluded that adalimumab showed superior efficacy compared with MTX and placebo. In the subanalysis of the CHAMPION trial, it was seen that PASI75 was achieved by 70% patients who were early responders to MTX (i.e. those who achieved PASI50 at week 8) and by 41% patients who were late responders to MTX (i.e. who achieved PASI50 at week 12). Less than 5% of patients who were late non-responders achieved PASI 75 [Reich et al. (2010), in Dogra and Mahajan (2013)] (11). Hence, patients who do not respond to MTX by week 12 may be considered for alternative therapy.

In another trial comparing subcutaneous briakinumab (a monoclonal antibody against the p40 molecule) and oral MTX, the former was found to be significantly superior to MTX in terms of efficacy, although the risk of infection and malignancy was also slightly higher [Fallah Arani et al. (2011), in Dogra and Mahajan (2013)] (11). If the trials comparing biologicals and MTX are critically analysed, it is apparent that in all

these trials, MTX was initially started at the lower dose, which was increased to a maximum of 15–25 mg/week only when there was an unsatisfactory response. Because the efficacy of MTX may be dose-dependent [Montaudie et al. (2011) in Dogra and Mahajan (2013)] (11), the low initial dose of MTX may be responsible for the relatively lower number of patients achieving PASI 75 at week 12. In Indian trials, MTX has shown excellent efficacy and faster response with few side-effects when given at a dose of 0.3–0.5 mg/kg/week, hence, a comparison of the biological therapies with the full therapeutic dose of MTX given from the outset may be warranted.

Combination therapy

Methotrexate may be combined with psoralen ultraviolet A therapy (PUVA) [Morison et al (1982) in Warren et al (2008)] (14), ultraviolet B therapy (UVB) [Paul et al (1982), Armstrong et al (1982) in Warren et al (2008)] (14) and etretinate [Vanderveen et al (1982) in Warren et al (2008)] (14). The aim of such combinations being to reduce dosage and subsequent toxicity, however, concerns over the potential for cancer induction, with methotrexate and phototherapy [Fitzsimons et al (1983)], and hepatitis, with methotrexate and retinoids [Gollnick (1996)] has limited such approaches [in Warren et al (2008)] (14). Colchicine has been combined with methotrexate for treatment of generalized pustular psoriasis [Horiguchi et al (1981) in Warren et al (2008)] (14).

Methotrexate has also been combined successfully with cyclosporine in patients with severe, recalcitrant psoriasis, most of which had psoriatic arthropathy [Clark et al (1999) in Warren et al (2008)] (14). This allowed reduction in dosages of both drugs, and few adverse events were recorded during the study. More recently, a prospective study of 20 patients severely affected with psoriasis on this combination of therapies found the treatment effective with limited manageable toxicity [Aydin et al (2006) in Warren et al (2008)] (14). The combination has not been studied in the long term.

## 2.4.3. Discussion on clinical efficacy

No new studies have been provided specifically to address the efficacy in the moderate recalcitrant psoriasis population. The presented information either refers to combined "moderate to severe" population, or simply to patients with psoriasis, with or without arthritis.

A discussion about published studies in patients with moderate to severe psoriasis / psoriatic arthritis is provided, supported by study narratives and meta-analyses. Most of the discussion in the clinical overview is based on the Eurogioderm guideline for the systemic treatment of psoriasis from Nast et al., published in 2022.

No raw data from the discussed studies has been provided. This does not facilitate the discrimination of efficacy in moderate psoriasis from the efficacy in severe psoriasis, for which a risk benefit has already been considered positive and authorised.

Extension of the indication from severe to moderate to severe psoriasis would thus consider the discussion of the added benefit and risk of the moderate psoriasis population. Of note, injectable methotrexate has already been approved via Decentralized Procedure (RMS SE + 22 CMSs) with the "moderate to severe psoriasis" indication. Therefore, extension of the indication for which a risk benefit has been considered positive would be based on similar grounds.

During the procedure, the MAH was asked to discuss available data in moderate psoriasis, and its comparison to the data available in severe psoriasis. This included:

a) The operational definition of moderate psoriasis. The PASI has a significant inter-observer variability, and patients who score 5-10 with some investigators may score higher with others,

making the PASI 10 point cut-off a very debatable, at least in earlier trials, where investigator training was not common.

b) The data on moderate as compared to severe psoriasis population in available studies

c) The adequacy of extrapolation of efficacy on severe psoriasis patients observed in the presented studies, to the moderate population, should it not be able to fulfil b).

The provided studies did not discriminate between these populations, and thus, it was considered that the data performed covered both the moderate and the severe populations.

Additionally, although not requested by the MAH, a simplified indication "are indicated for patients with moderate-severe plaque psoriasis" was suggested by CHMP, removing the "recalcitrant disabling" wording. This is in line with previously approved systemic biological therapies. It was considered that the indication wording "'who are candidates for systemic therapy'' better reflects definition of patient severity and population and is in line with recent approvals from CHMP.

### 2.4.4. Conclusions on the clinical efficacy

Considering the totality of evidence provided by the applicant the CHMP considered the extension of indication in patients with moderate psoriasis approvable.

## *2.5. Clinical safety*

### Introduction

No new clinical data have been provided in this application. A review of relevant clinical data literature is presented by the MAH.

### Patient exposure

Overall, here is a known difference between high-dose methotrexate as used in neoplastic diseases which frequently cause AEs and SAEs, and low-dose methotrexate treatment (including rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease and psoriasis patients). Low dose therapy is well tolerated in the majority of patients.

Nevertheless, the toxicity spectrum in low dose treated patients is widespread with respect to symptoms and intensity, including serious and sometimes fatal cytopenia, pneumonitis and liver disease. Careful patient selection and regular monitoring as well as doses adapted to the actual needs of the patients are essential to reduce the toxicity of MTX in low-dose methotrexate treatment [Albrecht et al (2010)] (1).

There were no new trials presented, so there is no new exposure in CT.

**Post-authorisation experience**

The patient exposure is calculated by using the assumed average maintenance dose per day (WHO DDD) of 2.5 mg for MTX used for non-oncologic indications in adults, given by the WHO Collaborating Centre for Drug Statistics Methodology. The weekly average dose is 2.5 mg x 7 = 17.5 mg.

The MAH has used the WHO DDD for non oncology indications, but this pertains to 17.5 mg per week, whilst the recommended dose for Nordimet is 15 mg per week. As such, the exposure is estimated to be 267 627 patient treatment years.

## Adverse events

A review of adverse events from the literature for antineoplastics and psoriatic indications is performed below.

Antineoplastics indication

The acute effects of antineoplastic drugs often include nausea and vomiting, sometimes extremely severe.

In addition, many of these compounds are irritant or vesicant, and produce local pain, irritation, and inflammation at the administration site; extravasation may lead to ulceration and necrosis. Hypersensitivity reactions may also occur.

Many of the adverse effects of antineoplastics are an extension of their therapeutic action, which is generally not selective for malignant cells but affects all rapidly dividing cells: antineoplastic therapy is then made possible only by increased sensitivity or less effective recovery of malignant cells compared with normal cells, and dosage is carefully controlled and timed, and, where possible, localized, to maximize the differences. In consequence, adverse effects may be expected from most antineoplastics in tissues where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastrointestinal mucosa, skin, and gonads, as well as in the foetus. The effects may not manifest for days or weeks, depending both on the rugs used and the rate of division in the tissue concerned, and may sometimes be cumulative. Because of their effects on the various types of white blood cells, many antineoplastics also cause profound suppression or normal immunity, and patients may be at greatly increased risk of severe and disseminated infection.

The rapid destruction of large numbers of cells during antineoplastic therapy of certain highly sensitive tumours, and the consequent release of breakdown products may also lead to problems with hyperuricaemia and acute renal failure due to uric acid nephropathy (the ' tumour lysis syndrome').

In the very long term, patients who have undergone successful anti neoplastic chemotherapy may develop secondary malignancies, suggesting that antineoplastics may themselves be carcinogenic. In addition, most are potentially mutagenic and teratogenic, and use in pregnancy, particularly in the first trimester, may lead to foetal abortion, stunting, or malformation [Martindale (2020c)].

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.

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. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given.

Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgia, necrosis of soft tissue and bone, and anaphylaxis.

Purpuric skin lesions due to vasculitis have occurred after both high dose [Navarro et al (1986), in Martindale (2014a)] (29), and low dose [Marks et al (1984), Tomer et al (1997) Martindale (2020a)] (6). Accelerated rheumatoid nodulosis has been reported [Williams et al (1998), Filosa et al (1999) in Martindale (2020a)] (6) after the use of methotrexate in patients with rheumatoid arthritis. Erosion of psoriatic plaques, accompanied by pain and erythema, has been seen' after low-dose methotrexate therapy; blistering and necrosis consistent with toxic epidermal necrolysis has occurred [Reed et al (1983) in Martindale (2020a)] (6). Possible exacerbation of a photosensitivity reaction to ciprofloxacin has been described, [Nedorost et al (1989), in Martindale (2020a)] (6) and reactivation of sunburn has also been reported [Khans et al (2000) in Martindale (2020a)] (6) several in cases where methotrexate was given within 2 to 5 days after the initial sunburn.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors, it is teratogenic, and it has been associated with foetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned [Martindale (2020a)]. (6)

Low dose therapy

*Table 9 Tables and summaries provides a listing of adverse drug reactions provided by [eMC-50 (2014]. (7)*

| Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data) | | |
|---|---|---|
| **Gastrointestinal disorders** | Very common | Stomatitis, dyspepsia, nausea, loss of appetite,vomiting, abdominal pain, inflammation and ulcerations of mucous membrane of mouth and throat, (especially during the first 24-48 hours after administrati on of Methotrexate 25 mg/ml) |
| | Common | Diarrhoea (especially during the first 24-48 hours after administration of Methotrexate 25 mg/ml) |
| | Uncommon | Gastrointestinal ulcers and bleeding. |
| | Rare | Enteritis, melaena Gingivitis, malabsorption |
| | Very rare | Haematemesis, toxic megacolon |
| **Skin and subcutaneous tissue disorders** | Common | Exanthema, erythema, itching |
| | Uncommon | Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque (Psoriatic lesions can exacerbate due to UV radiation during concomitant treatment with methotrexate (also see section 4.4); severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's syndrome). |
| | Rare | Increased pigmentary changes of nails, onycholysis, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions |
| | Very rare | Acute paronychia, furunculosis, telangiectasia hidradenitis |
| **General disorders and administration site conditions** | Uncommon | After intramuscular use of methotrexate, local adverse reactions (burning sensation) or damage (sterile formation of abscess, destruction of fatty tissue) can occur at the site of injection, disturbed wound healing. |
| | Very rare | Fever, Subcutaneous administration of methotrexate shows good local tolerance. Only mild local skin reactions, the number of which decreased in the course of treatment, have been observed so far. |
| **Immune system disorders** | Uncommon | Allergic reactions, anaphylactic shock |
| | Very rare | Immunosuppression Hypogammaglobulinaemia |
| **Metabolism and nutrition disorders** | Uncommon | Diabetes mellitus |
| **Nervous system disorders** | Common | Headache, fatigue, drowsiness |
| | Uncommon | Vertigo, seizures |
| | Very rare | Pain, muscular asthenia or paresthesia of the extremities, changes in sense of taste (metallic taste), acute aseptic meningitis with meningism (paralysis, vomiting) |
| | Unknown | Leukoencephalopathy |
| **Eye disorders** | Rare | Severe visual disturbances |
| | Very rare | Conjunctivitis, retinopathy |
| **Hepatobiliary disorders** | Very common | Increase in liver-related enzymes (ALAT [GPT], AST [GOT], alkaline phosphatase and bilirubin). |
| | Uncommon | Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); drop of serum albumin. |
| | Rare | Acute hepatitis |
| | Very rare | Hepatic failure |
| **Cardiac disorders** | Rare | Pericarditis, pericardial effusion, pericardial tamponade |
| **Infections and infestations** | Very rare | Sepsis, infections (incl. reactivation of inactive chronic infection) may be fatal in some cases |
| **Vascular disorders** | Rare | Hypotension, thromboembolic events |
| **Respiratory, thoracic and mediastinal disorders** | Common | Pulmonary complications due to interstitial alveolitis/pneu monitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. |
| | Uncomon | Pulmonary fibrosis |

| | | |
|---|---|---|
| | Rare | Pharyngitis, apnoea, bronchial asthma-like reactions with cough, dyspnoea and pathological findings in the lung function test |
| | Very rare | Pneumocystis carinii pneumonia and other pulmonary infections, chronic obstructive pulmonary disease, pleural effusion |
| **Blood and lymphatic system disorders** | Common | Leukopenia, anaemia, thrombocytopenia |
| | Uncommon | Pancytopenia, agranulocytosis, haematopoietic disorders |
| | Very rare | Severe courses of bone marrow depression, aplastic anaemia, lymphadenopathy, lymphoproliferative disorders (partly reversible), |
| **Renal and urinary disorders** | Uncommon | Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria |
| | Rare | Renal failure, oliguria, anuria, azotaemia |
| | Very rare | Proteinuria |
| **Reproductive system and breast disorders** | Uncommon | Inflammation and ulceration of the vagina |
| | Rare | Oligospermia, menstruation disorders |
| | Very rare | Loss of libido, impotence, , vaginal discharge, infertility gynaecomastia |
| **Musculoskeletal and connective tissue disorders** | Uncommon | Arthralgia, myalgia, osteoporosis |
| | Rare | Stress fracture |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | Uncommon | Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas |

The appearance and degree of severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is necessary for patients to be monitored regularly at short intervals.

Psoriasis

In a review by Warren et al (2008) (14), nausea, stable leukopenia and mild elevation of liver transaminases are listed as common and manageable side effects of methotrexate.

Rarely, hematopoietic suppression can be significant, particularly as a result of overdosing of methotrexate [Roenigk et al (1988) in Warren et al (2008)] (14). Rare severe bone marrow suppression can also be due to compromised renal function or drug interactions [Shupack et al (1988) in Tung et al (1990)] (12). Despite its rapid cellular activity, effects on bone marrow have been rare. According to McKinnon et al (1985) [in Benedek (2010)] (30), only seven instances of leukopenia and three of pancytopenia had been reported as of 1985, to which they added six cases of pancytopenia, two being fatal [McKinnon et al (1985) in Benedek (2010)] (30). Bone marrow injury appears to be related to renal failure. Anagen alopecia, oral ulceration, and cutaneous erosions are rare when a weekly dosing schedule is used [Kaplan et al (1988) in Warren et al (2008)]. (14)

Other rare complications include cutaneous ulceration [Kaplan et al (1988)], ataxia [Baker (1970b)], folliculitis, reactivation of tuberculosis [Smith et al (1971)], depression and other psychotic symptoms [Baker (1970b)], [all in Warren et al (2008)]. (14)

The incidence of central nervous system toxicity from low-dose methotrexate therapy is quite rare. The most common complaints include headache and dizziness [Kremer et al (1988), Nyfors (1978), Weinblatt et al (1985, 1988), Wernick et al (1989) in Tung et al (1990)] (12).

Individuals who consume alcohol while on methotrexate, are diabetic, and/or are obese are more likely to develop significant liver toxicity. Hepatotoxicity is also a major concern in long term methotrexate therapy [Coe et al (1968), Roenigk el a1 (1988), Weinstein el al (1973) in Tung et al (1990)] (12). Toxicity leading to cirrhosis appears to be the result of total cumulative dose of the drug and not the duration of therapy [Weinstein et al (1973) in Tung et al (1990)] (12). The weekly dosing schedule has been shown to have a lower incidence in promoting pathological changes than the daily dose regimen [Menard et al (1980), Roenigk et al (1969) in Tung et al (1990)]. (12)

Hepatotoxicity is the major problem of low dose pulse methotrexate therapy in patients with psoriasis [Roenigk et al (1998) in Grim et al (2003)] (31). Elevation of hepatic enzymes, especially transaminases, occurs in about 20% of patients shortly after initiation of low dose pulse methotrexate therapy, but generally resolves within 1-3 weeks of treatment. However, the risk of developing severe hepatotoxicity (grade III or IV) occurs later and has been reported in approximately 3-25% of psoriatic patients [Roenigk et al (1998), Olsen (1995) in Grim et al (2003)] (31). Malatjalian et al (1996) [in Maryles et al (2003)] (9) reported a 23.1 % incidence of severe hepatotoxicity, including severe hepatic fibrosis and liver cirrhosis, in patients treated with long-term methotrexate for psoriasis. However, patients with rheumatoid arthritis on low dose pulse methotrexate therapy rarely develop severe hepatotoxicity [Roenigk et al (1998), Olsen (1995) in Grim et al (2003)]. (31)

Roenigk et al (1998) [in Warren et al (2008)] (14) have published recommendations on methotrexate therapy for psoriasis and suggest liver biopsy at a cumulative dose of 1.5 g. According to Hashkes et al (1997) [in Gutierrez-Suarez et al (2010) (32)], routine invasive liver biopsies are not necessary in patients with juvenile rheumatoid arthritis since several studies have shown no long-term adverse effects or liver fibrosis in patients treated for a mean of 3.5 to 5 years [Haskes et al (1997) in Gutierrez-Suarez et al (2010)] (32). Liver biopsy is only indicated if pre-existing or a recently acquired liver disease is found [Nieuhues et al (2006) in Gutierrez-Suarez et al (2010)] (32).

Liver biopsy is associated with significant comorbidity and rarely mortality; therefore, novel noninvasive ways to monitor for hepatotoxicity have been explored. Three monthly monitoring of serum levels of the aminoterminal propeptide of type III collagen (pIIINP) may allow 70% of patients to be monitored without liver biopsy [Zachariae et al (1989), Boffa et al (1996), Zachariae et al (2001) in Warren et al (2008)] (14).

Other rare but important complications include pulmonary fibrosis/alveolitis, infection, osteopathy, and mutagenicity. Methotrexate osteopathy presents as a triad of severe pain localized to the distal tibia, osteoporosis, and compression fractures of the distal tibia. Withdrawal of methotrexate appears to be the only treatment [Zonneveld et al (1996) in Warren et al (2008)] (14).

Two patterns of methotrexate-induced pulmonary disease have been reported [Carson et al (1987) in Tung et al (1990)] (12). The first is a hypersensitivity reaction characterised by interstitial pneumonitis, granuloma formation and the development of bronchopneumonia; the second, a toxic drug reaction with diffuse alveolar damage and other signs of nonspecific lung injury [Phillips et al (1986, 1987), Rail et al (1963) in Tung et al (1990)] (12).

Especially in patients with rheumatoid arthritis, low dosage methotrexate therapy can induce interstitial lung injury. The X-ray film generally shows linear and reticulonodular basal and/or midlung field infiltrates. A biopsy specimen shows monocellular cell desquamation into the alveoli, along with a tendency to form non-caseating granulomas that contain multicellular giant cells. About 40% of patients have concomitant eosinophilia and 17% have a rash [Olsen (1991) in Grim et al (2003)] (31). The strongest predictor for lung injury is old age (≥60 years), diabetes mellitus, rheumatoid pulmonary involvement, previous use of DMARDs and hypoalbuminaemia [Alarcon et al (1997) in Grim et al (2003)] (31). Many reports describe opportunistic infections caused by Pneumocystis carinii in patients on low dose pulse methotrexate therapy.

Several reports associate these infections with pancytopenia [Jeurissen et al (1989), Al-Awadhi et al (1993), Basin et al (1991) in Grim et al (2003)] (31), whereas others describe pulmonary infection only [Thomas et al (1986), Groenendal et al (1990), Stewart et al (1990) in Grim et al (2003)] (31). Very often, these patients are elderly with decreased creatinine clearance and infections of the urinary tract treated with cotrimoxazole/trimethoprim-sulfamethoxazole.

Once pulmonary toxicity is suspected, treatment with methotrexate should be withheld [Tung et al (1990)].

MTX does not seem to affect the lung in children with juvenile idiopathic arthritis and therefore, pulmonary function tests are usually not necessary in those patients [Schmeling et al (2002) in Gutierrez-Suarez et al (2010)] (32).

As a known teratogen [Warkany (1978) in Tung et al (1990)] (12) methotrexate should not be used in pregnant women. For the same reason, methotrexate should not be given to females of childbearing potential. Contraceptive measures [Hatcher et al (1988-89)] should be employed in patients of childbearing age, and continue for 12 weeks after stopping therapy [Hanna et at (1980), Roenigk et al (1988), Voorhees et al (1969)], [all in Tung et al (1990)] (12).

Males should also be advised to use contraception while on methotrexate therapy and for 3 months after completing treatment. Reversible oligospermia has been observed in male patients receiving methotrexate therapy, but the drug does not seem to affect ovarian functions [Jolivet et al (1983), Shamberger et al (1981), Sussman et al (1980) in Tung et al (1990)] (12). Because of the S-phase-specific action of the drug, the slowly dividing spermatogonial stem cells are not expected to be affected. The actively dividing spermatocytes and spermatids, on the other hand, are influenced by the action of methotrexate, thus suppressing spermatogenesis [Shamberger et al (1981), Sussman et al (1980) in Tung et al (1990)] (12). There is no evidence of irreversible harmful effects of methotrexate on the testes, and male patients treated with the drug at the time of conception have produced normal offspring [Perry (1983) in Tung et al (1990)] (12).

Methotrexate carries a theoretical risk of carcinogenesis. Indeed, there has been a report of metastasizing squamous cell carcinoma of the skin in a psoriasis patient on long-term methotrexate therapy [Jensen et al (1989) in Warren et al (2008)] (14).

Furthermore, long-term follow-up of a cohort of patients on PUVA and other therapies for psoriasis has suggested a relative risk of 2:1 for squamous cell carcinoma of the skin in those who have had high-dose methotrexate exposure vs low or no exposure [Stern et al (1994) in Warren et al (2008)] (14). This risk was independent of PUVA, and thus, close surveillance of psoriasis patients on long-term methotrexate therapy is advisable.

Supplementation with folic and folinic acids

Folate deficiency and methotrexate toxicity share some similar symptomatology. Depleted intracellular folate levels have been documented in hepatocytes and peripheral blood lymphocytes of methotrexate-treated patients with rheumatoid arthritis [Kremer et al (1986), Morgan et al (1991) in Bannwarth et al (1994)] (33). Initial plasma homocysteine levels, an indicator of folate status, were found to be predictive of future toxicity during methotrexate therapy in folate unsupplemented patients [Morgan et al (1991) in Bannwarth et al (1994)] (33). It was therefore postulated that folate supplementation would be useful in reducing some of the toxic manifestations associated with low dosage methotrexate therapy [Bannwarth et al (1994)] (33).

Folic acid 1mg daily was shown to reduce methotrexate toxicity without compromising its efficacy in rheumatoid arthritis [Morgan et al (1990) in Bannwarth et al (1994)] (33). An uncontrolled long term trial provided indirect evidence that the incidence of nausea, diarrhoea, stomatitis, and liver function abnormalities may be lowered by folic acid 7mg weekly [Stewart et al (1991b) in Bannwarth et al (1994)] (33). Clinical studies reveal a decrease of about 50% in reported adverse effects in rheumatoid arthritis patients receiving supplementation therapy, especially with respect to nausea and fatigue [Morgan et al (1990), Shiroky et al (1993) in Grim et al (2003)] (31). In an open study, high dosage calcium folinate (45 mg/week) was reported to be effective in preventing methotrexate-related nausea, but this benefit

was overshadowed by the worsening of the disease activity [Tishler et a1 (1988) in Bannwarth et al (1994)] (33). Calcium folinate 1 mg taken simultaneously with methotrexate had no obvious effect on either the disease activity or on methotrexate toxicity [Weinblatt et al (1993a) in Bannwarth et al (1994)] (31). Conversely, calcium folinate 2.5 or 5 mg/week decreased the common adverse effects of methotrexate, including transaminase elevations, oral ulcers, and gastrointestinal symptoms, without interfering with its efficacy. In this study, calcium folinate was given 24 hours after the weekly oral dose of methotrexate 7.5 to 30mg [Shiroky et al (1993) in Bannwarth et al (1994)] (33).

In double-blind, placebo-controlled studies in adults with rheumatoid arthritis, 1-5 mg of folic acid led to a significant reduction in adverse effects while preserving the efficacy of methotrexate therapy. However, in order to preserve the anti-inflammatory effect a slightly higher dosage of methotrexate was necessary [Ortiz et al (1998), Van Ede et al (2001) in Niehues et al (2006)] (10). Moreover, in adults with rheumatoid arthritis folic acid supplementation lowers homocysteine levels, which are increased during low-dose methotrexate [Morgan et al (1998), Van Ede et al (2002) in Niehues et al (2006)] (10). It seems that folic acid supplementation is associated with a reduced methotrexate discontinuation rate in adults [Harten (2005) in Niehues et al (2006)] (10).

Folic acid (l mg/day) application in children with juvenile rheumatoid arthritis has been studied in a double-blind, placebo-controlled, crossover study and has not affected anti-inflammatory efficacy [Hunt et al (1997) in Niehues et al (2006)] (10).

However, in this study there were no systematic data on toxicity, there was a rather small cohort of 19 children with juvenile idiopathic arthritis, and the observation period was very short (13 weeks). Therefore, it is difficult to deduce a recommendation based on this study. Huemer et al (2003) [in Niehues et al (2006)] (10) studied the effect of folic acid supplementation and methotrexate treatment on homocysteine levels in children. They showed that patients with juvenile idiopathic arthritis receiving methotrexate have significantly elevated baseline plasma homocysteine levels compared with age- and sex-matched healthy control individuals but that there is no significant impact of folate supplementation on homocysteine levels. Thus, in patients with minor adverse effects with methotrexate the use of folic acid at a dosage of 1 mg/day is feasible [Niehues et al (2006)] (10).

For psoriasis patients, addition of folic acid (5 mg daily) can help to alleviate gastrointestinal side effects, and close monitoring of liver function and full blood count allow continued therapy in most.

A recent study has suggested that folic acid supplementation may reduce the treatment efficacy of methotrexate in the control of psoriasis [Salim et al (2006) in Warren et al (2008)] (14). However, the total numbers in this study were small, and firm conclusions not possible. Currently, it is recommended that psoriasis patients on methotrexate therapy should have supplemental folic acid at 5 mg/d including the day of methotrexate dosing [Strober et al (2005) in Warren et al (2008)] (14).

Not only the dosage of folate, but also the timing of the dose may play a role. When a dose of calcium folinate equal to the methotrexate dose was given 4 hours after methotrexate administration, the efficacy of methotrexate did not change, and the incidence of stomatitis and gastrointestinal toxicity tended to decrease [Buckley et a1 (1990) in Bannwarth et al (1994)] (33). A single dose of calcium folinate 20 mg weekly administered midway between weekly doses (5 to 25 mg, mean 18.5 mg) of methotrexate had no adverse effects on disease control [Hanrahan et al (1988) in Bannwarth et al (1994)] (33). In contrast, calcium folinate 15mg given 2 hours after methotrexate caused exacerbation of rheumatoid arthritis [Joyce et al (1991) in Bannwarth et al (1994)] (33). In these 2 studies, there was no difference between placebo and calcium folinate regarding methotrexate-induced adverse effects [Bannwarth et al (1994)] (33). Also Van Ede et al (1998) [in Grim et al (2003)] (31) observed that late administration of folic acid, i.e. 3 to 4 days after methotrexate, was no more effective than placebo in controlling nausea.

Furthermore, folate supplementation did not reduce the incidence of postoperative infectious complications in methotrexate-treated patients [Perhala et al (1991) in Bannwarth et al (1994)] (33).

Bressolle et al (2000) [in Grim et al (2003)] (31) reported increases of methotrexate total clearance and volume of distribution in patients taking folic acid supplementation therapy. This observation was interpreted as increased cellular uptake of methotrexate, with the folic acid supplements promoting the intracellular sequestering of methotrexate. It is also possible that the reduced AUC is associated with increased intracellular folate levels.

Folinic acid may also be used for oral supplementation therapy. If doses of low dose pulse methotrexate are 5-12.5mg weekly, 2.5mg of folinic acid is administered the day after LDMTX. If the dose is 15-30mg weekly, the amount of folinic acid is increased to 5mg, given the day after methotrexate [Roenigk et al (1998), Shiroky (1997) in Grim et al (2003)] (31).

**Post marketing experience**

## Serious adverse event/deaths/other significant events

Local tolerance

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy [eMC-50 (2014)] (7).

The product under consideration Methotrexate 25 mg/ml solution for injection will be supplied in prefilled pen containing volumes in a range of 0.3 ml to 1.0 ml. The reference product Lantarel FS from Pfizer is supplied in prefilled syringes with volumes in the range of 1 ml to 2.67 ml. Several other product strengths of methotrexate are marketed including Metoject 50 mg/ml solution for injection of Medac.

## Safety in special populations

Paediatric population: The product is indicated for the treatment in adult patients in this indication.

Notwithstanding, the Applicant has provided observational data on efficacy and safety (Bronckers et al, 2020) on 187 paediatric patients treated with MTX, either isolated or in combination or sequentially with biologicals. In a follow up between 1 to 5 years, the efficacy and safety patterns did not differ significantly from what has been observed in adults.

Elderly population (treatment of psoriasis)

Much lower doses of methotrexate are effective in controlling psoriasis in the elderly, probably as a consequence of reduced renal clearance. Patients older than 80 years have been adequately controlled on only 2.5 mg of methotrexate per week [Fairris et al (1989) in Warren et al (2008)] (14).

It is prudent to accept that some residual areas of psoriasis will remain to prevent relative over treatment. Complete clearance of psoriasis should not be a goal of treatment. Although the use of methotrexate can have fatal consequences, most of such cases are attributable to absolute or relative overdosage [Baker (1970) in Warren et al (2008)] (14).

Patients with renal impairment

Patients with renal impairment have a higher overall rate of toxicity for a variety of drugs. The risk of severe toxicity is increased about 4-fold in patients with renal impairment. Concomitant use of other potentially nephrotoxic drugs, including NSAIDs, and preexisting renal insufficiency are additional risk factors. Therefore, although direct toxicity of low dose MTX has not been proven, the dosage regimen should be adjusted in patients with severe renal impairment [Albrecht et al (2010)] (1).

Before starting MTX therapy and for monitoring, investigation of serum creatinine with creatinine clearance and serum albumin assay should be obtained once a month for the first 3 months, then every 4-12 weeks [Pavy et al (2006) in Albrecht et al (2010)] (1).

Methotrexate is not generally considered nephrotoxic when used at low doses for inflammatory disease, although renal impairment is reported [Kremer et al (1995) in Nast et al. (2022)] (13). Methotrexate and 7-hydroxymethotrexate are mainly excreted through the kidneys, via glomerular filtration and active transport. Methotrexate clearance is therefore reduced (and thus risk of toxicity increased) in the context of chronic kidney disease, depending on the stage. In a cohort of 77 patients with RA and various stages of chronic kidney disease, the elimination half-life of a single dose of intramuscular methotrexate (7.5-15 mg) was directly related to glomerular filtration rate, with a decrease in methotrexate of 44.7 % in the category of patients with the poorest renal function (i. e., creatinine clearance < 45 ml/min, roughly equivalent to stage 3b) [Bressolle et al (1998) in Nast et al. (2022)] (13). Pooling data from randomised clinical trial of methotrexate for RA also indicates that presence of renal impairment (creatinine clearance < 79 ml/min) increases the odds ratio for severe and pulmonary toxicity by four compared to those with a creatinine clearance > 99.8 ml/min (reference group) [Rheumatoid Arthritis Clinical Trial Archive Group (1995) in Nast et al. (2022)] (13).

### Safety related to drug-drug interactions and other interactions

No specific information was provided, regarding the interested population.

### Discontinuation due to adverse events

The information provided did not allow to discriminate the AEs that led to discontinuation nor the timing of discontinuation in psoriasis indication vs the other indications or severity. This did not prevent full assessment of the safety considering the well-known safety profile of methotrexate.

## 2.5.1. Discussion on clinical safety

The MAH has not provided a discussion regarding the frequency of AEs in any population with psoriasis: neither moderate, nor moderate to severe, neither with nor without arthritis. A reference has been made to risk factors for hepatotoxicity in the psoriasis indication. It is understood that the baseline characteristics of the patients in several studies (such as BMI> 30 in up to 30% of pts) may increase the frequency of identified AEs, both in methotrexate and comparator arms.

Upon request from CHMP, the safety profile in the moderate psoriasis population has been discussed as compared to the "moderate to severe" population. In the presented studies, moderate population has not been discriminated from the severe population. It is understood that the safety profile in the moderate to severe psoriasis population should not differ from the pooled safety characteristics that have been presented by the MAH. This takes also into consideration the associated risk factors in the psoriatic population, such as the cardiac, metabolic, and hepatic comorbidities. Therefore, it is adequate to consider that the safety profile of the population with moderate psoriasis should not be significantly different from the severe population.

The MAH has provided a discussion on special populations which are not a particular concern on the interested one. The SmPC adequately mentions the safety profile of the moderate to severe psoriasis patient population.

### 2.5.2. Conclusions on clinical safety

Although no new adverse reactions has been identified in the interested population, it was considered important to understand if the moderate psoriasis population had a similar safety pattern as the severe population. Upon request, the MAH provided a detailed discussion on both efficacy and safety of the product of both RCTs, observational studies and of SmPCs of similar approved products. The data shows that in the presented studies, moderate to severe patients were analysed altogether, thus not being able to discriminate among them. Thus, it is adequate to support that the previously discussed frequency, seriousness or other characteristics of the AEs which are valid to "moderate" should also be valid to "moderate to severe" population.

### 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/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 8 is acceptable.

### *Safety concerns*

*Table 10* ***Summary of the Safety Concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Haematological toxicity<br>Hepatotoxicity<br>Pulmonary toxicity<br>Renal toxicity<br>Medication error due to inadvertent daily instead of weekly dosing |
| Important potential risks | None |
| Missing information | Exposure in children younger than 3 years old |

## *Pharmacovigilance plan*

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection in the form of a targeted follow-up questionnaire is conducted for the following risk: medication error including overdose from inadvertent daily instead of weekly dosing.

No additional pharmacovigilance activities are undertaken.

## *Risk minimisation measures*

*Table 11 Description of routine risk minimisation measures by safety concern*

| Safety concern | Routine risk minimization activities |
|---|---|
| Haematological toxicity | Routine risk communication:<br>Warning in sections 4.4, 4.5 and 4.8 of the SmPC<br>Contraindication in section 4.3 of the SmPC<br>Warning in section 2 and 4 of the PL<br><br>Specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:<br><br>Section 4.4 SmPC: Before and during treatment patients should undergo a complete blood count with differential blood count and platelets<br>Section 2 of PL: Doctor will conduct blood tests to check for abnormalities developing in the blood<br><br>Other routine risk minimization measures beyond the Product Information:<br>Restricted medical prescription |
| Hepatotoxicity | Routine risk communication:<br>Warning in sections 4.2, 4.4, 4.5 and 4.8 of the SmPC<br>Contraindication in section 4.3<br>Warning in section 2 and 4 of the PL<br><br>Specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:<br><br>Section 4.4 SmPC: - Before and during MTX therapy liver function tests should be conducted. In addition, closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.<br>Section 2 of PL: Before treatment is started your doctor may carry out blood tests, and also check how well your kidneys and liver are working.<br><br>Other routine risk minimization measures beyond the Product Information:<br>Restricted medical prescription |
| Pulmonary toxicity | Routine risk communication:<br>Warning in sections 4.4 and 4.8 of the SmPC<br>Warning in section 2 and 4 of the PL<br><br>Specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:<br>Section 4.4 SmPC: - Before initiating therapy a chest X-ray must be conducted. During therapy assessment of the patient's respiratory system should be monitored as outlined in the product information.<br><br>Section 2 of PL: Before treatment is started your doctor will request a chest x-ray.<br><br>Other routine risk minimization measures beyond the Product Information:<br>Restricted medical prescription |
| Renal toxicity | Routine risk communication:<br>Contraindication in section 4.3<br>Warning included in sections 4.2, 4.4, 4.5 and 4.8<br>Warning in section 2 and 4 of the PL |

| | |
|---|---|
| | Specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:<br>Section 4.4 SmPC: Before and during treatment patients should undergo renal function tests and urianalysis. In addition, closer monitoring is required in case of possible renal impairment (e.g. in elderly patients).<br><br>Section 2 of PL: Before treatment is started your doctor will check how well the kidneys are working<br><br>Other routine risk minimization measures beyond the Product Information:<br>Restricted medical prescription |
| Medication errors due to inadvertent daily instead of once weekly dosing | Routine risk communication:<br>Boxed warning in section 4.2 of the SmPC<br>Warning in sections 4.4 and 4.8 of the SmPC<br>Warning in sections 2 and 3 of the PL<br><br>Specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:<br>Section 4.2 SmPC: A boxed warning that is approved and proposed indication, MTX must only be used once per week<br><br>Section 2 of PL: Boxed warning reminding patients to take medication once per week.<br>Other routine risk minimization measures beyond the Product Information:<br>Restricted medical prescription<br><br>A visual reminder on the outer, intermediate and immediate packaging to warn patients to take the product once a week for those indications requiring dosing once a week. |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2 and 4.9 of the SmPC have been updated.

Consequently, the PL is also updated.

### 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:

The additional indication wording impacts only sections 1 and 3 of the PL, the rest of the PL wording remains the same.
It is considered that the additional indication wording does not introduce any new safety message and does not in any way impact the readability of the leaflet. Therefore, no further readability testing is required.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull-red scaly plaques, particularly on extensor parts of limbs and in the scalp. The pathogenesis of psoriasis is still incompletely understood.

Psoriasis is a disabling disease and may even be life-threatening on rare occasions. Psoriasis affects 1.5 to 3% of the general population in Europe. The first manifestation of psoriasis may occur at any age. Two peaks of onset are frequently reported: in the second and third decades and about the age of 60. In 3% of patients, psoriasis begins in childhood. Patients with a family history of psoriasis tend to have an earlier age of onset. The duration may vary from a few weeks to a whole lifetime. The clinical course is unpredictable but in the majority of cases psoriasis is a chronically remitting and relapsing disease.

Chronic stable plaque psoriasis (psoriasis vulgaris) is the commonest form of the disease, accounting for 85-90 % of cases. The circumscribed infiltrated skin lesions are scaly and erythematous and often symmetrically distributed over the body.

### 3.1.2. Available therapies and unmet medical need

Topical corticosteroids are commonly used for mild to moderate cases. Other topical medications include keratolytic agents, anthralin, coal tar, vitamin D analogs, and retinoids. For more widespread disease, phototherapy (ultraviolet B [UVB] or psoralen with ultraviolet A [PUVA]) is commonly used. Systemic therapy, including methotrexate (MTX), cyclosporine, synthetic retinoids, and fumaric acid are often effective in patients with moderate or severe disease. Apremilast, an oral selective inhibitor of the enzyme phosphodiesterase 4, is also approved for the treatment of psoriasis. Biological therapies have emerged as an alternative treatment option for patients with moderate to severe psoriasis in need of systemic therapy. Expression of tumour necrosis factor (TNF)-induced proteins in psoriatic plaques provided the rationale for the development of TNF-neutralizing therapies for psoriasis, and the anti-TNF agents etanercept, adalimumab, and infliximab are approved for the treatment of moderate to severe psoriasis. Ustekinumab, a p40 IL 12/23 inhibitor, is approved for the treatment of moderate to severe psoriasis. More targeted biological therapies such as guselkumab and risankizumab, IL-23 inhibitors and anti-IL-17 monoclonal antibodies such as brodalumab, ixekizumab, and secukinumab are also available with higher results in terms of PASI 90 (about 70-75% at week 16). These more targeted therapies such as IL-17 and IL-12/23 inhibitors have added incremental clinical benefit.

### 3.1.3. Main clinical studies

There were no new studies to support the updated indication. The applicant included literature references and bibliographic research.

## *3.2. Favourable effects*

Methotrexate has been used in a moderate to severe psoriasis population. In this population with a broad range of seriousness level, efficacy regarding soft and robust endpoints (namely PASI 75) has been described between 14 and 60%. Start of effect, duration, maintenance of effect have not been discussed

to a great detail. However, in trials lasting more than 9 months, there seems to a plateau in the improvement phase, followed by a decrease phase.

Not all presented studies discriminate the PASI reduction. Where available, the level of PASI 75 reduction as presented in literature ranged between 9 and 82.7% in moderate to severe psoriasis (32 studies), and between 50 and 92% in the severe population (11 studies). The frequency of published moderate to severe patients reaching PASI 100 was between 4.5 and 18% and in severe patients PASI 100 ws observed in between 30 to 69%.

Start of effect, duration, and maintenance of effect have not been discussed, but in general for trials lasting more than 9 months, there seems to exist a plateau in improvement around week 24, followed by a decrease.

The MAH has presented data upon request of the CHMP, which support the fact that the discrimination between mild and moderate is usually clear and surely clearer than the discrimination between moderate and severe populations. Moreover, in the studies discussed, the "moderate to severe" population PASI / BSA scores has shown that most patients were within the moderate expected boundary.

## *3.3. Uncertainties and limitations about favourable effects*

The degree of response and maintenance of effect in the moderate population cannot be clearly distinguished from the literature, however it can be derived from the METOP study (Warren, 2017) (18). These study data are considered sufficiently robust to demonstrate the effect of methotrexate in the "moderate to severe" population. However, the uncertainty remains regarding the degree of response and maintenance of effect in the moderate population.

The population to be added to the presently approved indication [i.e. moderate psoriasis] lacks precise definition. A PASI score between 5-10 is usually considered to be representing the "moderate" population, but as there is high inter-rater variability with PASI, a patient scored as mild for some clinicians may easily be upgraded to moderate by other clinicians. In clinical trials, severity of the condition is usually more precise, and clinicians are trained to the study inclusion criteria. In the post-marketing setting, defining the "moderate" condition is not easy between patients, slightly symptomatic not needing systemic treatment, and more severe patients which require systemic treatment with immunomodulators and where the benefit outweighs the known safety risks. Thus, the request of widening of the indication to moderate patients may in practice extend the indication to patients that would be considered mild for some prescribers.

## *3.4. Unfavourable effects*

The safety profile in the moderate to severe population seem not to differ in the nature of AEs. No clear information on frequency, seriousness, time to event or risk factors was available for the moderate population.

## *3.5. Uncertainties and limitations about unfavourable effects*

In the severe psoriasis treated patients, serious adverse events have been reported, in line with what has been described for low dose methotrexate for other conditions. Moderate patients may be less willing to accept some adverse events to get the disease under control as they would if they were severe patients. Moderate patients tend to have a shorter disease duration, be younger and with an expected longer treatment duration. Thus, methotrexate exposition would likely be different. Notwithstanding, the data which supported the severe indication, was mostly based upon analysis of the "moderate to severe"

population, which mostly comprised of moderate patients. Therefore, the discussion on a different safety pattern between moderate and severe populations becomes theoretical but not confirmed in practice.

## 3.6. Effects Table

*Table 12* ***Effects Table for [Nordimet]***

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PASI75 response | PASI75 treatment responders by mth 9 | % | MTX 67.8% | - | Lack of control. | Appani et al. (2019) |
| EULAR response | EULAR DAS28 ESR moderate + good response by mth 9 | % | MTX 80.8% | - | Lack of control | Appani et al. (2019) |
| **Unfavourable Effects** | | | | | | |
| Frequency of AEs | Frequency of AEs | % | MTX 31% | Apremilast 38.1% | Circa 16 week duration | Ki et al. (2021) |

## 3.7. Benefit-risk assessment and discussion

### 3.7.1. Importance of favourable and unfavourable effects

The favourable effects in the moderate population have not been individualized nor quantified. Still, given that most studied patients were in the "moderate" band of the spectrum, data available for the "moderate to severe" band should adequately cover and be similar to the "moderate" band, allowing a B/R assessment in moderate psoriasis.

The unfavourable effects have also not been discriminated in the "moderate" population. Again, given the burden of moderate patients in the studies which studied patients "moderate to severe", the unfavourable profile should be similar.

### 3.7.2. Balance of benefits and risks

The information presented for both efficacy and safety on the extended population (moderate psoriasis patients), allows the maintenance of the positive B/R balance in moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## 3.8. Conclusions

The proposed extension of the indication in plaque psoriasis from the severe population to the "moderate to severe" population is approvable.

# 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 treatment of moderate psoriasis in adults who are candidates for systemic therapy based on literature; As a consequence, sections 4.1, 4.2 and 4.9 of the SmPC were updated. The Package leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted.

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 Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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

## Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

## *Paediatric data*

Not applicable.

# 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 EMEA/H/C/003983/II/0027

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