COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Methotrexate Basic Pharma 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection in a pre-filled syringe 37.5 mg/ml

(methotrexate)

NL/H/5217/001-011/MR

Date: 25 October 2021

This module reflects the scientific discussion for the approval of Methotrexate Basic Pharma 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection in a pre-filled syringe 37.5 mg/ml. The procedure was finalised at 5 February 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
AUC	Area under the plasma drug concentration–time curve
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
JIA	Active juvenile idiopathic arthritis
MAH	Marketing Authorisation Holder
NSAIDs	Non-steroidal anti-inflammatory drugs
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Methotrexate Basic Pharma 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection in a pre-filled syringe 37.5 mg/ml, from Basic Pharma Manufacturing B.V.

The product is indicated for the treatment of:

- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- severe recalcitrant disabling psoriasis vulgaris, which is not adequately responsive to therapy, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

A comprehensive description of the indications and posology is given in the SmPC.

The product is already registered nationally in the Netherlands. The national products are duplexes of the medicinal products of Methotrexate BPM 5-30 mg, solution for injection 37,5 mg/ml (NL/H/4085/001-011/DC).

This mutual recognition procedure concerns a hybrid application claiming essential similarity with the European reference product (ERP) Lantarel FS solution for injection from Pfizer Pharma PFE GmbH. The innovator product has been authorised in Germany since November 1991.

The concerned member state (CMS) involved in this procedure was Poland.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. Compared to the innovator product Lantarel FS, the proposed products are developed to be identical with respect to the active substance, pharmaceutical form, therapeutic indication and route of administration. However, the proposed medical products are not identical with respect to the used concentration since this concentration is 25 mg/ml for Lantarel FS and 37.5 mg/ml for Methotrexate.

II. QUALITY ASPECTS

II.1 Introduction

Methotrexate Basic Pharma, solution for injection in pre-filled syringe is a clear yellowish solution, pH 7.0 to 9.0, with an osmolality of approximately 250 mOsm/kg.

Each ml solution contains 37.5 mg methotrexate.

- Each syringe of 0.133 ml contains 5 mg methotrexate.
- Each syringe of 0.200 ml contains 7.5 mg methotrexate.
- Each syringe of 0.267 ml contains 10 mg methotrexate.
- Each syringe of 0.333 ml contains 12.5 mg methotrexate.
- Each syringe of 0.400 ml contains 15 mg methotrexate.
- Each syringe of 0.467 ml contains 17.5 mg methotrexate.
- Each syringe of 0.533 ml contains 20 mg methotrexate.
- Each syringe of 0.600 ml contains 22.5 mg methotrexate.
- Each syringe of 0.667 ml contains 25 mg methotrexate.
- Each syringe of 0.733 ml contains 27.5 mg methotrexate.
- Each syringe of 0.800 ml contains 30 mg methotrexate.

In addition, these medicines contain less than 1 mmol sodium (23 mg) per ml, that is to say essentially “sodium-free”.

The solutions are put in pre-filled syringes of colourless glass (type I) of 1 ml capacity with a chlorobutyl rubber plunger, fitted with a safety system containing a polypropylene plunger rod.

Methotrexate Basic Pharma are available in packs of one prefilled syringe with embedded subcutaneous injection needle with safety system. The filling volumes and colour codes for the different strengths are as follows:

Strength	Volume	Colour code
5 mg	0.133 ml	White
7.5 mg	0.200 ml	Red
10 mg	0.267 ml	Green
12.5 mg	0.333 ml	Light blue
15 mg	0.400 ml	Purple
17.5 mg	0.467 ml	Pink
20 mg	0.533 ml	Burgundy
22.5 mg	0.600 ml	Dark green
25 mg	0.667 ml	Dark blue
27.5 mg	0.733 ml	Yellow
30 mg	0.800 ml	Orange

The excipients are sodium chloride, sodium hydroxide, hydrochloric acid (for pH adjustment) and water (for injections).

II.2 Drug Substance

The active substance is methotrexate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Methotrexate is a yellow or orange, crystalline, hygroscopic powder. The drug substance is practically insoluble in water, in 96% ethanol and

in methylene chloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates. The drug substance shows polymorphism; however, as the pharmaceutical form of the finished product is a solution, polymorphism is not a critical attribute.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with relevant European guidelines. The excipients are well known and common in parenteral formulations. The composition is qualitatively the same as for the reference products.

In view of the *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*, the volume of the syringe is considered acceptable for use in children. Pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process is a non-standard process, consisting of preparation of the solution, sterile filtration, and filling. No sterilization in the final container is performed. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the products have been presented for three bulk batches, each divided and filled into the strengths of 5 mg, 7.5 mg and 30 mg, in accordance with the relevant European guidelines.

Control of excipients
All excipients are of Ph.Eur. quality. The specifications are acceptable.

Microbiological attributes
The manufacturing process is an aseptic process. The batches produced so far all show compliance to the Ph.Eur. sterility test, both at release and during stability testing. Validation reports on microbiological testing, bacterial endotoxin testing and sterility demonstrate that the methods are suitable for their intended use.

Quality control of drug products
The finished products specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, extractable volume, visible and sub visible particles, assay, impurities, uniformity of mass, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength of 5 mg, 7.5 mg and 30 mg from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug products
Stability studies according to ICH stability conditions were performed at accelerated (40°C/75% RH, six months), intermediate (30°C/65% RH, 12 months) and long-term (25°C/60% RH, 18 months) storage conditions on the 5 mg, 7.5 mg and 30 mg product strengths. For each strength, three batches in the primary packaging material were tested. Out of specification results were observed for a specified impurity at six months at accelerated conditions for all batches in the stability studies, whereas the same specified impurity results at intermediate and long-term storage conditions were within specification. On basis of the data submitted, a shelf life was granted of 18 months. The labelled storage conditions are: 'store below 30°C, do not refrigerate or freeze, and store in the outer carton in order to protect from light for the drug product.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the products, nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Methotrexate Basic Pharma have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Methotrexate Basic Pharma are intended for substitution of similar methotrexate products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are hyrbid formulations of Lantarel FS which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The active substance methotrexate is a well-known substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

Methotrexate Basic Pharma 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection in a pre-filled syringe 37.5 mg/ml is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered intramuscular or subcutaneous, when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved (NfG CPMP/EWP/QWP 1401/98).

In this case, both the proposed products and reference products are aqueous solutions having the same qualitative composition with as only difference the concentration of the

product, i.e. 37.5 mg/ml (proposed product) versus 25 mg/ml (reference product). Thus, the volume of solution to be injected will differ between the products. The available literature indicates that the difference in the injected volume as much as five-fold does not affect the exposure of methotrexate, but slightly affects the maximum concentration (C_{max}), i.e. administration of 50 mg/ml of methotrexate resulted in similar total exposure in terms of the area under the plasma drug concentration–time curve (AUC), but a somewhat higher C_{max} (15-20% higher), compared with the lower strength (10 mg/ml) following both intramuscular and subcutaneous administration. This difference in C_{max} was however considered clinically irrelevant in perspective of individual dose titration. The difference in injection volume of the test product is less than two-fold, compared to the reference product. Therefore, it can be expected that this difference in injection volume will not affect the AUC, but it could potentially result in a 15-20% higher C_{max}. However, this difference is not considered clinically relevant. Therefore, a biowaiver for the Methotrexate 37.5 mg/ml products is considered acceptable.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Methotrexate Basic Pharma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lantarel FS. A biowaiver has been granted, and no new clinical studies were conducted. Risk management is adequately addressed.

Overall, Methotrexate Basic Pharma can be considered as therapeutic equivalent, with the same efficacy and safety profile as known for the active substance of the reference medicinal products. The current products can be used instead of its reference products.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of a pilot test followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Methotrexate Basic Pharma 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection in a pre-filled syringe 37.5 mg/ml have a proven chemical-pharmaceutical quality and are hybrid forms of Lantarel FS solution for injection. Lantarel FS is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Methotrexate Basic Pharma with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 5 February 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5217/1-011/IA/001	Type IA B.IV.1.a.1 - Change of a measuring or administration device; Addition or replacement of a device which is not an integrated part of the primary packaging Conditions Documentation Procedure type; 1. Device with CE marking	No	26-04-2021	Approved	
NL/H/5217/1-011/IB/002	Type IB B.II.f.b1 – Change in the shelf-life or storage conditions of the finished product; As packaged for sale (supported by real time data)	PL, SmPC	16-06-2021	Approved	
NL/H/5217/1-011/IB/003	Type IB B.II.d.1d – Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	No	24-06-2021	Approved	
NL/H/5217/1-011/IB/004	Type IB B.II.e.5a – Change in pack size of the finished product; Change in the number of units (e.g. tablets, ampoules, etc.) in a pack	PL, SmPC	07-07-2021	Approved	

	Change outside the range of the currently approved pack sizes				