COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Methotrexate BPM 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, 30 mg, solution for injection

(methotrexate)

NL/H/4085/011-001/DC

Date: 18 April 2019

This module reflects the scientific discussion for the approval of Methotrexate BPM. The procedure was finalised at 20 July 2018. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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
MAH	Marketing Authorisation Holder
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 BPM 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, 30 mg, solution for injection from Basic Pharma Manufacturing bv.

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lantarel FS 25 mg/ml solution for injection which has been registered in Germany by Pfizer Pharma PFE GmbH since 13 November 1991 (originator product). Nordimet 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg solution for injection (EU/1/16/1124) has been centrally registered since 18 August 2016.

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

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, since the concentration of the solution is different compared to the innovator product (25 mg/ml in Lantarel and 37.5 mg/ml for Methotrexate BPM solution for injection).

Scientific Advice was given by the Netherlands in 2012 and the MAH followed this.

II. QUALITY ASPECTS

II.1 Introduction

Methotrexate BPM is a clear yellowish solution for injection, in a pre-filled syringe, with pH 7.0 - 9.0, and osmolality of approximately 250 mOsm/kg. The solution contains as active substance 37.5 mg/ml methotrexate.

The solution is packed in pre-filled syringes of colourless glass of 1 ml capacity, with embedded s.c. injection needle with a safety system. A range of prefilled syringes are

available, containing different volumes of the solution and therefore containing different amounts of methotrexate per syringe:

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

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients are well known and common in parenteral formulations. The composition is qualitatively the same as for the reference product.
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. The aseptic manufacturing process has been justified in view of *Draft Guideline on Sterilisation of the medicinal product, active substance, excipient and primary container*.
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 product have been presented for three bulk batches in accordance with the relevant European guidelines.

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

Quality control of drug product
The finished product 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 BET. 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 product
Stability studies according to ICH stability conditions, at accelerated (40°C/75% RH, 6 months), intermediate (30°C/65% RH, 12 months) and long-term (25°C/60% RH, 18 months) storage conditions are performed on 5 mg, 7.5 mg and 30 mg, three batches of each

strength, in the primary packaging material. Out of specification results were observed for a specified impurity at 6 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 product 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 BPM has 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 BPM is intended for generic substitution, 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

This product is a hybrid formulation 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

Methotrexate BPM is a well-known active 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 BPM 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, 30 mg, solution for injection 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 as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98).

In this case, both products are watery solutions having the same qualitative composition with the only difference in amount of the concentration of the product to be developed, i.e. 37.5 mg/ml (Test) vs 25 mg/ml (Reference). Thus, also 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 5-fold does not affect the exposure of methotrexate but slightly affects C_{max}, i.e. administration of 50 mg/ml of methotrexate resulted in similar total exposure in terms of AUC, but somewhat higher C_{max} (15-20% higher), compared with the lower strength (10 mg/ml) following both i.m. and s.c. 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 compared to the Reference product is less than the 2-fold and therefore it can be expected that this difference in the injection volume will not affect the AUC but it could potentially result in at most 15-20% higher C_{max}. This difference however is not considered clinically relevant. A biowaiver for Methotrexate BPM 37.5 mg/ml is considered acceptable.

Therefore, Methotrexate BPM may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 BPM.

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

Important identified risks	• Medication error, including overdose from inadvertent daily instead of weekly dosing • Liver impairment • Kidney impairment • Acute or chronic interstitial pneumonitis • Blood toxicity • Teratogenicity/administration during pregnancy and lactation • Immunosuppression • Increased risk of neoplasms • Encephalopathy/leukoencephalopathy
Important potential risks	• Infertility • Dosing error inpatients who switch from another methotrexate-containing product
Missing information	• Use in children below three years of age

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. No new clinical studies were conducted. This application is different from the reference product in strength. Similarity to the reference product has been sufficiently demonstrated based on submitted literature. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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 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 BPM 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, 30 mg, solution for injection has a proven chemical-pharmaceutical quality and is a hybrid form of Lantarel FS. Lantarel FS solution for injection is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The application was discussed in the Board meeting of 5 July 2018. Questions were raised regarding the sterilisation process of the final drug product, process validation and stability. Subsequently sufficient data were provided regarding these quality issues. Overall, the Board concluded that the benefit-risk balance for this medicinal product is positive.

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 BPM with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 July 2018.

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/4085/001-011/IB/002	Change in supplier of packaging components or devices (when mentioned in the dossier) - to replace the safety device in the dossier - this safety device is different from the one already approved and therefore it is not the replacement of a supplier but rather the replacement of a type of safety device	--	7-3-2019	Approved	--