CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Methotrexaat ADOH 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg, solution for injection in pre-filled syringe ADOH B.V., the Netherlands

methotrexate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2607/001-008/DC
Registration number in the Netherlands: RVG 111626, 111766-111772

25 September 2013

Pharmacotherapeutic group:	antineoplastic agents; antimetabolites - folic acid analogues
ATC code:	L01BA01
Route of administration:	intravenous, intramuscular, subcutaneous
Therapeutic indication:	active rheumatoid arthritis in adult patients; polyarthritic forms of severe, active juvenile idiopathic arthritis; severe recalcitrant disabling psoriasis
Prescription status:	prescription only
Date of authorisation in NL:	1 August 2013
Concerned Member States:	Decentralised procedure with DK, FI, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Methotrexaat ADOH 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg, solution for injection in pre-filled syringe from ADOH B.V. The date of authorisation was on 1 August 2013 in the Netherlands.

The product is indicated for:

- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

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

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis and chronic polyarthritis, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lantarel FS 25 mg solution for injection in pre-filled syringes, which has been registered in Germany by Wyeth Pharma GmbH since 13 November 1992. The reference product in the Netherlands is Ledertrexate Forte 50 mg/2 ml, solution for injection (NL License RVG 06988), which was registered by Wyeth. This product was withdrawn from the Dutch market in 2002. However, the withdrawn Ledertrexate Forte product and the product Lantarel FS currently authorised in Germany belong to the same global marketing authorisation.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Methotrexaat ADOH solution for injection in pre-filled syringe is a product for parenteral use in aqueous solution, it is exempted from bioequivalence studies (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is methotrexate, an established active substances described in the European Pharmacopoeia (Ph.Eur.*). It is a yellow or orange, crystalline, hygroscopic powder, which is sparsely soluble in water and practically insoluble in ethanol and in methylene chloride.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual ethanol in line with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Methotrexaat ADOH is a clear, yellow solution with a pH of 8.0-9.0 and an osmolality of approximately 300 mOsm/kg. One ml of solution contains 25 mg methotrexate (as methotrexate disodium).

The solution is packed in pre-filled syringes of colourless glass (type I) of 1 ml capacity with attached injection needle and with a safety device to prevent needlestick injury and re-use. The plunger stoppers are made of chlorobutyl rubber.

Pack sizes:
Pre-filled syringes containing 7.5 mg (in 0.3 ml), 10.0 mg (in 0.4 ml), 12.5 mg (in 0.5 ml), 15.0 mg (in 0.6 ml), 17.5 mg (in 0.7 ml), 20.0 mg (in 0.8 ml), 22.5 mg (in 0.9 ml) and 25.0 mg (1.0 ml) methotrexate in solution for injection in packs of 1, 4 and 24.

The excipients are: sodium chloride, sodium hydroxide (for pH adjustment), water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients are well known. The drug product is an aqueous solution having the same qualitative composition and the same strength as the German reference product Lantarel FS 25 mg, prefilled syringe of 1 ml. Although the reference product uses the disodium salt of methotrexate whereas the test product includes methotrexate as a base, the drug product strengths are the same (*i.e.* 25 mg/ml).
The choice of the packaging and manufacturing process were justified. It was decided to sterilise the bulk solution by filtration and to fill syringes under aseptic conditions, since methotrexate is sensitive to degradation by heat. In-process controls for microbial contamination and bioburden are used. The choice of the sterilisation method is considered justified.
No clinical studies were performed. The drug product is essentially similar to the reference medicinal product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps in the process are the dissolution of the excipients, pH adjustment, filtration through two consecutive filters and aseptic filling and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale and three full-scale batches of the bulk solution that were filled into syringes to a volume of 0.3 ml and 1.0 ml respectively.

Control of excipients

The excipients comply with the requirements of the Ph.Eur. These specifications are acceptable.

Microbiological attributes

The drug product is a parenteral preparation and complies with the test for sterility (Ph.Eur.2.6.1) and bacterial endotoxins (Ph.Eur.2.6.14). The sterility of the product is guaranteed by the application of a suitable validated production process.

Quality control of drug product

The product specification includes tests for appearance, identification, extractable volume, pH, syringe integrity, sub-visible particles, visible particles, assay, related substances, uniformity of dosage units, sterility and bacterial endotoxins. The shelf-life requirements are identical to the release limits. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches of 0.3 ml fill volume and three full-scale batches of 1.0 ml fill volume, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three pilot-scale batches of 0.3 ml fill volume and three full-scale batches of 1.0 ml fill volume stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended commercial packaging. At all three storage conditions an increase of one impurity is seen that is most pronounced and leading to an out-of-specification after 6 months storage at accelerated conditions (40°C/75% RH). No other impurities were detected at any of the storage conditions. Furthermore, a significant change in assay is seen after 18 months at long-term and after 6 months at accelerated storage conditions. At all three storage conditions a slight increase in pH is seen that is most pronounced at accelerated conditions. No trends or changes are seen in any of the other parameters tested. Except for an increase of one impurity at accelerated conditions all tested parameters remained within the specified limits. The results of forced degradation studies demonstrated that methotrexate is sensitive to light in solution.
A shelf-life of 12 months has been granted with the storage condition ‘Store below 30°C’ and ‘Keep the syringe in the outer carton in order to protect from light’.

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.2 Non-clinical aspects

This product is a generic formulation of Lantarel FS, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of methotrexate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Methotrexate 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.

Methotrexaat ADOH 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg, solution for injection in pre-filled syringe 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). The qualitative composition of Methotrexaat ADOH is the same as the originator. Therefore, it 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. The pre-filled syringes with fixed needle are only suitable for intramuscular and subcutaneous administration.

Risk management plan
Methotrexate was first approved in 1962, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of methotrexate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC has been brought in line with the established texts of other methotrexate DCPs and compared with the originator texts for Metoject 50 mg/ml (SE/H/0643/DC), along with editorial changes with regard to information intended for medical or healthcare professionals. The SPC is agreed.

Readability test
The package leaflet has not been evaluated via a user consultation study. A waiver was applied for. The MAH indicated that the PIL under consideration is a copy of the PIL for Metoject 50 mg/ml solution for injection in pre-filled syringes, authorised during procedure SE/H/0643/001/DC. A comparison PILs was

submitted. The Metoject 50 mg/ml solution for injection in pre-filled syringes can however not be injected by patients themselves. Therefore, reference is made to the PIL for Clexane, authorised in the UK, which has been tested for readability in 2008. Based on this information, it is possible to waive consultation with target patient groups. Separate user testing for Methotrexaat ADOH is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Methotrexaat ADOH 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg, solution for injection in pre-filled syringe have a proven chemical-pharmaceutical quality and are a generic form of Lantarel FS 25 mg solution for injection in pre-filled syringes. 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.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Methotrexaat ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 June 2013. Methotrexaat ADOH 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg, solution for injection in pre-filled syringe were authorised in the Netherlands on 1 August 2013.

To comply with the PSUR synchronisation project, the MAH proposed an amended PSUR cycle to harmonise with the EU Harmonised Birth Date (1 January 1962) for all methotrexate containing medicinal products. The next Data Lock Point (DLP) of the PSUR will be June 2014.

The date for the first renewal will be: 10 June 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the ongoing stability studies and to submit the results of at least up to the proposed shelf life.
- The MAH committed to place the first three production batches on long-term stability studies through the proposed shelf-life and on intermediate stability studies for 12 months in accordance with the stability protocol.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached