COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Azitromycine ADOH 500 mg, powder for concentrate for solution for infusion

(azithromycin)

NL/H/4043/001/DC

Date: 1 March 2019

This module reflects the scientific discussion for the approval of Azitromycine ADOH 500 mg, powder for concentrate for solution for infusion. The procedure was finalised at 7 September 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 Azitromycine ADOH 500 mg, powder for concentrate for solution for infusion, from ADOH B.V.

The product is indicated in adults requiring initial intravenous therapy for the treatment of the following infections caused by azithromycin-susceptible pathogens:

- community-acquired pneumonia, including Legionnaires' disease
- Pelvic inflammatory disease (PID)

Note
In cases of severe pneumonia/ pneumonia requiring intensive care and/or prevailing risk factors, combination therapy (e.g. with a beta-lactam antibiotic) is required. Azithromycin monotherapy is not indicated for complicated infections, particularly infections in which azithromycin-resistant pathogens cannot be ruled out.

Consideration should be given to official guidance regarding the appropriate use of antibiotics.

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 Azitromax IV, 500 mg powder for solution for infusion which has been registered in France by Pfizer AB since December 2003. As no registration of Azitromax powder for solution for infusion containing azitromycine has been granted in the Netherlands, the French product is used as European Reference Product.

The concerned member states (CMS) involved in this procedure were Austria and Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Azitromycine ADOH is a whitish powder for concentrate for solution for infusion. One vial contains 500 mg of azithromycin powder (as dihydrate) equivalent to 100 mg/ml after reconstitution of a concentrate for solution for infusion. The reconstituted solution for infusion should have a final concentration of 1 mg azithromycin per ml.

The pH and Osmolarity of the product diluted with different diluents is listed below:

Diluted with	pH	Osmolarity (mOsmol/kg)
0.9% NaCl solution	6.6-6.8	287-298
0.45% NaCl solution	6.7-7.0	158-167
5% glucose solution	6.9-7.2	284-310
Ringer's lactate solution	6.6-6.8	266-272
5% glucose solution in 0.45% NaCl with 20 mEq KCl	6.6-6.7	451-458
5% glucose solution in Ringer's lactate solution	6.7	408-414
5% glucose solution in 0.3% NaCl	6.7-6.8	374-378
5% glucose solution in 0.45% NaCl	6.7	414-429

The powder packed in glass vials with rubber stopper and aluminium cap.

The excipients are: citric acid and sodium hydroxide.

II.2 Drug Substance

The active substance is azithromycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder and practically insoluble in water, freely soluble in anhydrous ethanol, acetone and methylene chloride. There is no question of polymorphism.

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 and meets the requirements of the monograph in the Ph.Eur. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 48 months 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 choice of excipients is justified and their functions explained. Since the product is a generic product for parenteral use containing the same amount of active substance and similar amounts of the same excipients, no bioequivalence study with the European reference product is required. The development studies included analysis of the composition and chemical properties of the reference product, followed by a comparison of the main characteristics of the proposed product and the reference product. The stability/compatibility studies on the reconstituted and diluted product are appropriately conducted at release as well as end of shelf-life.

Manufacturing process

The manufacturing consists of the compounding of the active and excipients, followed by sterile filtration of the bulk solution, which is aseptically filled into vials followed by lyophilisation. The process is adequately justified. Lyophilisation is considered a complex process and the manufacturing process is therefore considered to be a non-standard process. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients sodium hydroxide, citric acid, water for injections and nitrogen comply with Ph.Eur. requirements. 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, identity, completeness and clarity of solution, pH of reconstituted solution, water content, bacterial endotoxins, sterility, uniformity of dosage units, particulate contamination, related substances and assay. 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 full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scale batches stored at 25°C/60% RH (18 months), 30°C/75% RH (18 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 proposed commercial packaging. Photostability studies were performed in accordance with ICH recommendations on the powder and showed that the product is stable when exposed to light. Freeze thaw studies show no effect on short time exposures to low temperature. No significant changes were observed in any of the tested

parameters under both accelerated and long term storage conditions. All parameters remained within specifications. The proposed shelf-life of 24 months if stored in the approved packaging is acceptable. This medicinal product does not require any special storage conditions. The prepared solution is stable when it is stored at room temperature (≤30°C) for 24h or in refrigerator (2～8°C) for 7 days.

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 Azitromycine ADOH has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Azitromycine ADOH 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 generic formulation of Azitromax IV 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

Azithromycin 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

Azitromycine ADOH 500 mg, powder for concentrate for solution for infusion, 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). 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.

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 Azitromycine ADOH.

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

Important identified risks	- Serious allergic reactions, including angioedema and anaphylaxis (rarely fatal) - Hepatic failure - Pseudomembranous colitis - Use in patients with severe renal impairment (GFR < 10 ml/min) - Torsades de pointes and cardiac arrhythmia including ventricular tachycardia and prolonged QT interval of the electrodiogram - Exacerbations and new onset of myasthenia syndrome - Bacterial resistance - Superinfection with non-susceptible organisms
Important potential risks	- Concomitant use with ergotamine derivatives
Missing information	- Use during pregnancy and lactation

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 Azitromax IV. No new clinical studies were conducted. Risk management is adequately addressed. This generic 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 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

Azitromycine ADOH 500 mg, powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Azitromax IV, 500 mg powder for solution for infusion. Azitromax IV 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.

In the Board meetings of 4 October 2017 and 7 June 2018, the efficacy and risks of the product has been discussed. After adjustment of the indication and SmPC, the issues were resolved.

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 Azitromycine ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 September 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