COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Daptomycine Adoh 350 mg and 500 mg, powder for solution for injection/infusion (daptomycine)

NL License RVG: 128619 & 128621

Date: 8 May 2023

This module reflects the scientific discussion for the approval of Daptomycine Adoh 350 mg and 500 mg, powder for solution for injection/infusion. The procedure was finalised on 29 November 2022. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Daptomycine Adoh 350 mg and 500 mg, powder for solution for injection/infusion, from ADOH B.V.

The product is indicated for the treatment of the following infections (see sections 4.4 and 5.1 of the SmPC):

- Adult and paediatric (age of 1 year up to and including 17 years) patients with complicated skin and soft tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) caused by Staphylococcus aureus. It is recommended that the decision to use daptomycin should take into account the antibacterial sensitivity of the organism and be based on expert advice. See sections 4.4 and 5.1 of the SmPC.
- Adult and paediatric (age of 1 year up to and including 17 years) patients with Staphylococcus aureus bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, and in paediatric patients, use in bacteraemia should be associated with cSSTI.

Daptomycin is only active against Gram-positive bacteria (see section 5.1 of the SmPC). In mixed infections where the presence of Gram-negative and/or certain types of anaerobic bacteria is suspected, Daptomycin Adoh should be co-administered with appropriate antibacterial agents.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Cubicin 350 mg and 500 mg, powder for solution for injection/infusion (EU/1/05/328/001-2), registered in the EU by Merk Sharp & Dohme since 19-01-2006.

II. QUALITY ASPECTS

II.1 Introduction

Daptomycine Adoh is a light yellow to light brown freeze-dried cake or powder.

It contains as active substance either 350 mg daptomycine, which is reconstituted with 7 mL solution of 9 mg/mL (0,9%) sodium chloride, or 500 mg, which is reconstituted with 10 mL solution of 9 mg/mL (0,9%) sodium chloride. Both products' reconstitution result in a solution containing 50 mg daptomycine per millilitre.

The only excipient is sodium hydroxide.

The powder is packed in 20 ml clear glass (type 1) vials with rubber stoppers. The 350 mg strength has red aluminium caps and the 500 mg strength has blue aluminium caps.

II.2 Drug Substance

The active substance is daptomycine, an established active substance not described in any pharmacopoeia. Daptomycine is a yellow or yellowish powder. In this product, daptomycin is employed in anhydrous form without salt. Daptomycin exhibits stereoisomerism due to the presence of 13 chiral centres. Isomers are formed in the natural process of microbial metabolization, and the chemical structures of these isomers cannot be affected by the subsequent purification steps. The enantiomeric purity of the substance is controlled adequately.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Daptomycin is cyclic lipopeptide antibiotic, produced by Streptomyces roseosporus. The manufacturing process involves: culture of the Working Cell Bank (considered as starting material), fermentation, extraction and refining (freeze drying) of the active substance. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets in-house requirements. For some of the quality control tests, the methods described in the European Pharmacopoeia (Ph.Eur.) were used. Batch analytical data demonstrating compliance with all specifications have been provided for three commercial scale batches. The limits for endotoxins have been sufficiently justified. The limits for residual solvents are in accordance with ICH Q3C and are acceptable. The limit for microbial quality is based on Ph. Eur. 5.1.4 and is acceptable.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 18 months. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

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 drug product manufacturer controls the specific optical rotation and related substances (specified, unspecified and total impurities) in the drug substance specification in line with the ASMF.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production batches per strength, in accordance with the relevant European guidelines. Daptomycine Adoh is a sterile, lyophilized product, which is manufactured by aseptic processing. The manufacturing process consists of the preparation of a bulk solution of the drug substance and the excipients, followed by the sterilising filtration of the bulk solution, which is then filled in vials and lyophilised. The vials are then capped and labelled. The filter retention capacity and extractable substances from the filter have been adequately discussed.

Control of excipients

The choice of excipients have been sufficiently justified and their functions explained. The MAH has adopted the Ph.Eur. specifications for all excipients used in the process: sodium hydroxide, water for injection and nitrogen. These specifications are acceptable.

Microbiological attributes

Sterilizing filtration is adopted to sterilize the drug product; the provided justification is considered acceptable and sufficient. It is shown that the container closure system adequately protects the drug product from light and microbial contamination.

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, reconstitution solution (time and clarity), pH, related substances, assay, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. The risk for presence of nitrosamines in the drug product was considered negligible.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches of each strength 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 batches per strength stored in accelerated conditions at 25°C/60% RH (6 months) and in long-term conditions at 2°C - 8°C (24 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Although the content of one

impurity approached the limit, the results of all drug product batches in the stability program complied with the specification. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are to store the product in the fridge (2°C - 8°C).

In-use stability data have been provided demonstrating that the product remains stable after constitution for 12 hours at 20°C - 25 °C and for 48 hours at 2°C - 8°C.

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 MEB considers that Daptomycine Adoh 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 Daptomycine 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 Cubicin, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Daptomycine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Daptomycine Adoh 350 mg and 500 mg, powder for solution for injection/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). The quantitative composition of Daptomycine Adoh is entirely 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.

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 Daptomycine Adoh.

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

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB 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 Cubicin. 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) of the 350 mg strength 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 Dutch. The test consisted of 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. The leaflets of Daptomycine Adoh 350 mg and 500 mg are very similar. Therefore, it was decided that the results of the readability test for the 350 mg strength also cover the assessment of the readability of the 500 mg leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Daptomycine Adoh 350 mg and 500 mg, powder for solution for injection/infusion have a proven chemical-pharmaceutical quality and are generic forms of Cubicin 350 mg and 500 mg, powder for solution for injection/infusion. Cubicin 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Daptomycine Adoh with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 29 November 2022.

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
Type IA: A.4	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)	No	22-3-2023	Approved	N/A