COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Daptomycin ADOH 350 mg and 500 mg, powder for solution for injection/infusion (daptomycin)

NL/H/5803/001-002/MR

Date: 16 October 2024

This module reflects the scientific discussion for the approval of Daptomycin ADOH 350 mg and 500 mg, powder for solution for injection/infusion. The procedure was finalised on 8 August 2023. 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 Member States have granted a marketing authorisation for Daptomycin 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:

- Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice.
- Adult and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated with cSSTI.

A comprehensive description of the up-to-date 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 mutual recognition procedure, essential similarity is proven between the new product and the innovator product Cubicin 350 mg, and 500 mg powder for solution for injection or infusion, which has been registered in the European Union via a centralised procedure (EU/1/05/328).

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

II. QUALITY ASPECTS

II.1 Introduction

Daptomycin ADOH is a powder for solution for injection/infusion. It is a pale yellow to light brown, lyophilised cake or powder.

Each vial contains as active substance 350 mg or 500 mg of daptomycin.

The excipient is sodium hydroxide.

The powder for solution for injection/infusion is packed in 20 mL type I clear glass vials with 20 mm rubber stoppers and red (350 mg strength) or blue (500 mg strength) aluminium plastic overseals.

II.2 Drug Substance

The active substance is daptomycin, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Daptomycin is a fermentation product and it appears as a yellow or yellowish powder. It is freely soluble in water, slightly soluble in 96% ethanol, practically insoluble in trichloromethane, isopropanol, n-butanol and acetonitrile.

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

The manufacturing process consists of fermentation, extraction and freeze drying. 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. The following tests were performed: appearance, appearance of solution, identification, pH, water content, residue on ignition, specific optical rotation, bacterial endotoxins, microbial contamination, assay, related substances and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches per strength.

Stability of drug substance

Stability data on the active substance have been provided for three batches per strength in accordance with applicable European guidelines. 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 development focused mainly on obtaining a stable drug product equivalent to the reference product. The principles of Quality by Design (QbD) and Quality Risk Management (QRM) were used to develop a drug product which is therapeutically equivalent to the reference product. The generic formulation and the reference product have the same composition and same chemical-pharmaceutical parameters. The essential similarity between the two products is sufficiently shown.

In general the pharmaceutical development of the product has been adequately performed, the choice of excipients has been justified and their functions explained. The choices of the manufacturing process and packaging are sufficiently justified.

Manufacturing process

Daptomycin manufacturing process consists of the preparation of a bulk solution of the drug substance and the excipients in water, 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 process has been sufficiently described.

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.

Control of excipients

The excipients comply with the Ph. Eur. requirements. The tests used to control the excipients are performed according to pharmacopoeial procedures, with the exception of nitrogen for which USP and in-house methods are used. Nonetheless, a test for assay (with external standard) has been included in the specification of nitrogen. Compliance with Ph. Eur. requirements is therefore demonstrated. These specifications are acceptable.

Microbiological attributes

For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

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 time, clarity of solution, pH, uniformity of dosage units, water content, particulate contamination, assay, related substances, sterility and bacterial endotoxins. 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. A low risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches per 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 at 2-8°C (24 months) and 25°C/60% RH (6 months). The stability was tested in accordance with applicable European guidelines. For both strengths, test results of the photo-stability study for samples with primary packaging and samples packaged in carton showed all quality attributes conform to the corresponding acceptance criteria. The results indicate that the product is not sensitive to light, and the container closure system can guarantee the photo-stability of the product. On basis of the data submitted, a shelf life was granted of 24

months. The labelled storage condition is “Store in a refrigerator (2 °C – 8 °C)”. After finalisation of the mutual recognition procedure, additional data were provided and the shelf life was extended from 24 to 36 months (variation NL/H/5803/002/IB/003, see table on page 9).

The in-use stability study has been performed on two batches of daptomycin. In-use stability data have been provided demonstrating that the product remains stable for 12 hours at room temperature and 48 hours at 2-8 °C for both reconstituted and diluted solutions.

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

The following post-approval commitment was made:

- To tighten the limit of any unspecified impurity in the finished product from NMT 0.5 % to NMT 0.2%, at both release and shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Daptomycin ADOH is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

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

IV.2 Pharmacokinetics

Daptomycin 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Daptomycin 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 Daptomycin ADOH.

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

Important identified risks	None
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 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) 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 10 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

Daptomycin 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 or 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.

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 Daptomycin ADOH with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 8 August 2023.

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/5803/001-002/IB/002	Change in the specification parameters and/or limits of the finished product. Other variation.	No	22-11-2023	Approved	-
NL/H/5803/II/001/G	Change in the specification parameters and/or limits of the finished product. Change outside the approved specifications limits range. Addition of a new specification parameter to the specification with its corresponding test method. Tightening of specification limits.	No	14-03-2024	Approved	-
NL/H/5803/001-002/P/001	Artikel 61(3): update the PIL	Yes	11-04-2024	Approved	-
NL/H/5803/002/IB/003	Change in the shelf-life or storage conditions of the finished product. Extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	05-07-2024	Approved	-
NL/H/5803/IB/004/G	Change in the (invented) name of the	Yes	22-08-2024	Approved	-

	medicinal product. for Nationally Authorised Products.				