COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Daptomycine Lorien 350 mg and 500 mg, powder for solution for injection or infusion

(daptomycin)

NL/H/4241/001-002/DC

Date: 27 August 2019

This module reflects the scientific discussion for the approval of Daptomycine Lorien 350 mg and 500 mg, powder for solution for injection or infusion. The procedure was finalised at 1 May 2019. 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 Daptomycine Lorien 350 mg and 500 mg, powder for solution for injection or infusion, from Laboratorios Lorien S.L.

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.

Daptomycin is active against Gram positive bacteria only. In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, this product should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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 Cubicin 350 mg and 500 mg powder for solution for injection or infusion which has been registered in the EEA by Merck Sharp & Dohme B.V. since 19 January 2006 through a centralised procedure (EU/1/05/328).

The concerned member states (CMS) involved in this procedure were Germany, France and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Daptomycine Lorien is a pale yellow to light brown lyophilised powder. Each vial contains 350 mg or 500 mg daptomycin. One ml of the 350 mg strength provides 50 mg daptomycin after reconstitution with 7 ml of sodium chloride 9 mg/ml (0.9%) solution. One ml of the 500 mg strength provides 50 mg of daptomycin after reconstitution with 10 ml of sodium chloride 9 mg/ml (0.9%) solution.

The powder for solution for injection or infusion is packed in 15 ml type I colourless glass vials with a bromobutyl rubber stopper and a transparent flip-off cap for the 350 mg strength and an orange flip-off cap for the 500 mg strength.

The only excipient is sodium hydroxide (for pH adjustment).

II.2 Drug Substance

The active substance is daptomycin, an established active substance, not described in the European Pharmacopoeia (Ph.Eur.). Daptomycin is an amorphous yellowish powder and is very soluble in water over the pH range 1 - 10. It is a cyclic tridecapeptide comprised of several D-configured and non-proteinogenic amino acids, including L-kynurinine, L-ornithine and L-3-methylglutamic acid. The N-terminus is acylated with N-decanoyl fatty acid side chains. The C-terminal carboxylate is cyclised onto the hydroxyl group of Thr residue at position 4, resulting in a cyclic decapeptide core. The fermentation by *Streptomyces Roseosporus* leads only to a single stereoisomer.

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.

<u>Manufacturing process</u>
Daptomycin is produced from the fermentation of the microorganism *Streptomyces roseosporus*. After the fermentation by *Streptomyces roseosporus* the drug substance steps include filtration, concentration, purifications and lyophilisation. No class 1 organic solvents or heavy metal catalysts have been used in the production of Daptomycin. The drug substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH and includes requirements for the following tests: appearance, identification, pH, optical rotation, water content, heavy metals, sulphated ash; assay, related substances, residual solvents, bacterial endotoxins, and microbiological quality. The specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for eight batches stored at -20°C (up to 12 months), 5°C (18 months) and 25°C/60%RH (6 months). Based on the provided stability data, the requested retest period of 24 months, with the storage condition 20°C ± 5°C, is acceptable. Furthermore, it has been shown that shipment at 5°C ± 3°C can be performed as sufficient stability of the drug substance over 24 months at this temperature has been demonstrated.

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. The development was straightforward as the drug product only consists of the consists of the drug substance and sodium hydroxide for pH adjustment, just as the reference product. Development studies of the manufacturing process included optimisation of the production temperature, and optimisation of the concentration of the bulk solution. As Daptomycin is sensitive to temperature, aseptic filtration, followed by aseptic processing was selected to obtain a sterile final product, this method is also applied for the reference product, and is acceptable.

No *in vivo* or *in vitro* bioequivalence studies have been performed as Daptomycin Lorien is a parenteral drug product and contains the same amount of same active substance with reference product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of cleaning, sterilisation of the packaging materials, preparation of bulk solution, aseptic filtration and filling, lyophilisation, capping, labelling and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipient complies with specifications of the most recent version of the European Pharmacopoeia, and is tested according to the current compendial test procedures. The specification is 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, completeness and clarity, visible particulate matter and pH of the reconstituted solution, water content, uniformity of dosage units, assay, related substances, bacterial endotoxins, sterility and sub-visible particulate matter. The release and shelf-life limits are identical, except for assay and related substances for which the shelf-life limits are wider 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 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 commercial scaled batches stored at 5°C (24 months) and 25°C/60%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline, for drug products to be stored refrigerated. The batches were stored in Type I colourless glass vials with a rubber stopper and a flip-off cap. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Under long term conditions both conditions little change in the tested parameters is observed, however, staying well within specification. Based on the provided stability data, the proposed shelf-life of 2 years (24 months), with the storage condition "Store in a refrigerator (2°C – 8°C)" is acceptable.

Stability data have been provided demonstrating that the product remains stable for 48 hours at 2°C-8°C or for 12 hours at 25°C following reconstitution to a solution of 50 mg/ml and after further dilution to solutions ready for infusion with the concentrations of 7.0 mg/ml and 10 mg/ml.

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 Daptomycine Lorien 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 Lorien 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 member states 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 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

Daptomycine Lorien 350 mg and 500 mg, powder for solution for injection or 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 the product 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 Lorien.

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

Important identified risks	- Severe skeletal muscle toxicity - Reduced susceptibility to daptomycin in S. aureus - Peripheral neuropathy - Severe hypersensitivity reactions (including pulmonary eosinophilia and severe cutaneous reactions) - Eosinophilic pneumonia
Important potential risks	- Bone marrow toxicity - Severe hepatotoxicity - Dysregulation of in vivo coagulation
Missing information	- Patients with hepatic impairment - Pregnant or lactating women

The MAH shall ensure that all physicians who are expected to prescribe/use Daptomycin Lorien are provided with:

- Summary of Product Characteristics
- Dosage card

The dosage card should contain the following key messages:

- That there is a risk of severe skeletal muscle toxicity and so measuring the creatine phosphokinase at treatment initiation and at regular intervals is important. Patients at higher risk of developing myopathy should have more frequent creatine phosphokinase measurements.
- That Daptomycin Lorien can interfere with coagulation tests and this might lead to false results. To minimise this risk, physicians should be advised that for coagulation levels testing it is recommended to draw blood samples near the time of Daptomycin Lorien trough plasma concentration.
- The dosage card should contain the appropriate algorithms for calculating the Daptomycin Lorien dose for reconstitution, to help minimise the risk of medication errors (high osmolarity, overdose).

In addition, the MAH shall ensure that all laboratories expected to perform Daptomycin Lorien susceptibility testing are provided with:

- Summary of Product Characteristics
- Laboratory susceptibility testing leaflet

The laboratory susceptibility testing leaflet should contain the following key messages:

- That susceptibility testing minimises the risk of treatment failure by identifying strains with potential resistance to daptomycin.
- That daptomycin susceptibility testing needs calcium in the testing medium and testing methods with mediums providing consistent calcium concentrations are recommended.

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 test consisted of: a pilot test with 4 participants, followed by 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

Daptomycine Lorien 350 mg and 500 mg, powder for solution for injection or 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 Daptomycine Lorien with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 May 2019.

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