Public Assessment Report

Decentralised Procedure

Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion

(Daptomycin)

Procedure No: UK/H/6289/001-002/DC

UK licence Number: PL 08553/0580-0581

Dr Reddy's Laboratories (UK) Limited
LAY SUMMARY

Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion (Daptomycin)

This is a summary of the Public Assessment Report (PAR) for Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion (PL 08553/0580-0581; UK/H/6289/001-002/DC). It explains how Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion was assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products. These products will be referred to as Daptomycin throughout the remainder of this summary.

For practical information about using Daptomycin, patients should read the package leaflet or contact their doctor or pharmacist.

What is Daptomycin and what is it used for?

Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion are ‘generic medicines’. This means that Daptomycin is similar to ‘reference medicines’ already authorised in the European Union (EU) called Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion.

Daptomycin is used in adults and in children and adolescents (age from 2 to 17 years) to treat infections of the skin and the tissues below the skin. It is also used in adults to treat infections in the tissues that line the inside of the heart (including heart valves) which are caused by a bacterium called Staphylococcus aureus and to treat infections in the blood caused by the same bacterium when associated with skin or heart infection.

How does Daptomycin work?

The active substance in these medicines is Daptomycin. Daptomycin is an antibacterial that can stop the growth of certain bacteria.

How is Daptomycin used?

The pharmaceutical form of Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion is a powder of solution for injection or infusion and the route of administration is intravenous.

Daptomycin will usually be administered by a doctor or a nurse.

The dose will depend on the patient’s weight and the type of infection being treated. In adult patients, this dose is given directly into the blood stream (into a vein), either as an infusion lasting about 30 minutes or as an injection lasting about 2 minutes.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Daptomycin have been shown in studies?

No additional studies were needed as Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion are ‘generic medicines’ that contain the same active substance in the same concentration as the reference medicines, Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion. For this reason, Daptomycin is expected to be
bioequivalent with the reference medicine. Two medicines are considered bioequivalent when they produce the same levels of active substance in the body.

**What are the possible side effects of Daptomycin?**
Because Daptomycin is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine, Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion.

For the full list of all side effects reported with Daptomycin, see Section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

**Why is Daptomycin approved?**
It was concluded that, in accordance with EU requirements, Daptomycin has been shown to have comparable quality and is considered bioequivalent to Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion. Therefore, the MHRA decided that, for Daptomycin, the benefits are greater than the risks and recommended that these medicinal products can be approved for use.

**What measures are being taken to ensure the safe and effective use of Daptomycin?**
A Risk Management Plan (RMP) has been developed to ensure that Daptomycin is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.

**Other information about Daptomycin**
On 23 May 2017, Germany, Spain, France Italy, and the UK agreed to grant a Marketing Authorisation for Daptomycin. Following a subsequent national phase, a Marketing Authorisation was granted on 15 August 2017 in the UK.

The full PAR for Daptomycin follows this summary.

For more information about treatment with Daptomycin, read the package leaflet or contact a doctor or pharmacist.

This summary was last updated in September 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the application for Daptomycin Dr. Reddy’s 350 mg & 500 mg Powder for Solution for Injection/Infusion (PL 08553/0580-0581) could be approved.

These are decentralised abridged applications submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products, Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion, which were granted Marketing Authorisations to Novartis Europharm Limited on 19 January 2006 following a centralised procedure (EU/1/05/328/001-004). The Marketing Authorisation Holder of the reference products has been since been transferred to Merck Sharp & Dohme Limited.

Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion is a ‘prescription only medicine’ (legal status “POM”) containing the active substance daptomycin which is indicated for the treatment of the following infections:

- Adult and paediatric (2 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 patients with *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or 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, Daptomycin should be coadministered with appropriate antibacterial agent(s).

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

Daptomycin has a unique mechanism of action, killing Gram-positive bacteria by disrupting multiple aspects of bacterial plasma membrane function without penetrating into the cytoplasm. The drug exhibits rapid, concentration-dependent bactericidal activity in vitro against Gram-positive organisms, including enterococci. The MIC of daptomycin for antibiotic-susceptible strains is typically four-fold lower than that of vancomycin. Daptomycin produces a post-antibiotic effect (PAE) and regrowth times in vitro that are prolonged and concentration dependent. Spontaneous acquisition of resistance to daptomycin is rare.

No new non-clinical studies were conducted, which is acceptable given that these applications are for generic medicinal products based on reference products that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. In line with the CPMP ‘guideline on the investigation of bioequivalence’ subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98, a bioequivalence study was not necessary to support these applications, as both test and reference products are solutions at the time of administration.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications, and these are satisfactory.

The RMS and CMSs considered that these applications could be approved at the end of procedure on 23 May 2017. After a subsequent national phase, Marketing Authorisations were granted in the UK on 23 August 2017.
II QUALITY ASPECTS

II.1 Introduction
One vial of Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion contains 350 mg or 500 mg of daptomycin. The other pharmaceutical excipient is sodium hydroxide.

The finished products are packaged in a single use 15 ml type I glass vials with bromobutyl rubber stoppers and sealed with a 20 mm blue (500 mg) or yellow (350 mg) flip-off seal.

All primary product packaging complies with the current requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCES

Daptomycin

Chemical Name: N-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L-threonyl-glycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-threo-3-methyl-L-glutamyl-3-antraniloyl-L-alanine ε1-lactone

Structure:

Molecular Formula: C_{72}H_{101}N_{17}O_{26}

Molecular Weight: 1620.67 g/mol

Appearance: Daptomycin is a yellowish powder

Solubility: Daptomycin is very soluble in water. Daptomycin is also soluble in methanol and very slightly soluble in ethanol.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data that comply with the proposed specification are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate a powder for solution for injection or infusion containing Daptomycin 350 mg or 500 mg per vial, which are comparable in performance to the reference products, Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion (Novartis Europharm Limited). A satisfactory account of the pharmaceutical development has been provided.

The only excipient included in these medicinal products complies with a European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The applicant has confirmed that the manufacturing process has been validated at commercial scale.

Finished Product Specification

The finished product specifications are acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. In-house working standards are used, which are compared to European Pharmacopoeia references, where available. Representative Certificates of Analysis have been provided.

Stability

Stability studies for the finished products have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened product, with the storage condition, “Store in a refrigerator (2°C – 8°C)”.

After reconstitution: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours at 2°C – 8°C.
Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 24 hours at 2°C – 8°C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag) at 25°C must not exceed 12 hours (or 24 at 2°C – 8°C).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial at 25°C must not exceed 12 hours (or 48 at 2°C – 8°C). However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. Store in a refrigerator (2°C – 8°C).

Suitable post approval stability commitments to continue stability testing on batches of the finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended Marketing Authorisations are granted for Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion.

III NON-ClinICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance daptomycin are well-known. No new non-clinical data have been submitted for these applications and none are required. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new pharmacology data were submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted and none are required for applications of this type.

III.4 Toxicology
No new toxicology data were submitted and none are required for applications of this type.

III.5 Environmental Risk Assessment
Since these products will be used as substitutes for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.
III.6 Discussion on non-clinical aspects
It is recommended that Marketing Authorisations are granted for Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical studies have been performed and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics
In accordance with the CPMP guideline “Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 Corr ** - subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98”, no bioequivalence data have been submitted with this application and none are required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on clinical safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder has submitted an RMP, 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 Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion.

A summary of safety concerns, as approved in the RMP, are listed below:

### Summary of safety concerns

<table>
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<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
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<td>• Severe skeletal muscle toxicity</td>
<td>• Bone marrow toxicity</td>
<td>• Patients with underlying renal impairment</td>
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<tr>
<td>• Reduced susceptibility to daptomycin in S. aureus</td>
<td>• Severe hepatotoxicity</td>
<td>• Patients with hepatic impairment</td>
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<tr>
<td>• Peripheral neuropathy</td>
<td>• Dysregulation of in vivo coagulation</td>
<td>• Pregnant or lactating women</td>
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<td>• Severe hypersensitivity reactions (including pulmonary eosinophilia)</td>
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<tr>
<td>• Eosinophilic pneumonia</td>
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<tr>
<td>• Acute generalised exanthematous pustulosis (AGEP)</td>
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A summary of safety concerns, as approved in the RMP, are listed below:
The marketing authorisation holder also commits to these additional risk minimisation measures:

**Daptomycin dosage card**
The dosage card for daptomycin highlights the risk of developing severe skeletal muscle problems and provides dosing recommendations in special patient groups. It also gives guidance on how to minimise the interaction of daptomycin and particular reagents used in assay to determine the prothrombin time (PT) / international normalized ratio (INR).

**Susceptibility testing leaflet**
The susceptibility testing leaflet provides guidance for laboratories on how to perform susceptibility testing to get reliable test results, including the need for calcium in the testing medium. The susceptibility testing minimises the risk of treatment failure by identifying strains with potential resistance to daptomycin.

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion of the clinical aspects**
It is recommended that Marketing Authorisations are granted for Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion.

**V USER CONSULTATION**
A user consultation with target patient groups on the package leaflet has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**VI. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION**
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Daptomycin is considered to have demonstrated the therapeutic value of the compound. As these products are aqueous IV solutions at the point of administration, containing the same active substance and same concentration as the currently approved products Cubicin 350mg and 500mg Powder for Solution for Injection or Infusion, bioequivalence studies are not needed.

The benefit-risk is, therefore, considered to be positive.

**PRODUCT LITERATURE**
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The labelling for Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution for Injection/Infusion is found below:
Daptomycin Dr. Reddy's 350 mg & 500 mg Powder for Solution For Injection/Infusion

UK/H/6289/001-002/DC

For intravenous injection/infusion. Each vial contains 500 mg daptomycin. One ml provides 25 mg of daptomycin after reconstitution with 10 ml of sodium chloride 9 mg/ml (0.9%) solution. When administration is by injection reconstitute with 0.9% sodium chloride only.

Read the package leaflet before use. Store in a refrigerator (2°C - 8°C). Dr. Reddy's Laboratories (UK) Ltd.
Annex – Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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