26 January 2017
EMA/109959/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Daptomycin Hospira

International non-proprietary name: daptomycin

Procedure No. EMEA/H/C/004310/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Daptomycin Hospira
Applicant:	Hospira UK Limited Horizon Honey Lane Maidenhead Hurley SL6 6RJ UNITED KINGDOM
Active substance:	Daptomycin
International non-proprietary name/Common name:	Daptomycin
Pharmaco-therapeutic group (ATC Code):	other antibacterials (J01XX09)
Therapeutic indication(s):	Indicated for the treatment of the following infections (see sections 4.4 and 5.1). - 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. (see sections 4.4 and 5.1). - Adult patients with *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI. Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, daptomycin should be co-administered with appropriate antibacterial agent(s). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Pharmaceutical form:	Powder for solution for injection/infusion
Strengths:	350 mg (50 mg/ml) and 500 mg (50 mg/ml)
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial and 5 vials

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List of abbreviations

1.	API	Active Pharmaceutical Ingredient
2.	ASMF	Active Substance Master File = Drug Master File
3.	EC	European Commission
4.	ESI-MS	electrospray ionisation mass spectrometry
5.	EU	European Union
6.	GC	Gas Chromatography
7.	HPLC	High performance liquid chromatography
8.	ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
9.	IR	Infrared
10.	NMR	Nuclear Magnetic Resonance
11.	NMT	Not More Than
12.	Ph. Eur.	European Pharmacopoeia
13.	RH	Relative Humidity
14.	SmPC	Summary of Product Characteristics
15.	US	United States of America
16.	USP	United States Pharmacopoeia
17.	UV-VIS	Ultraviolet-visible spectrophotometry
18.	XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 8 February 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Daptomycin Hospira, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Daptomycin Hospira is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- *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. See sections 4.4 and 5.1.*
- *Adult patients with Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI.*

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

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Cubicin instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less

than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Cubicin, 350 mg and 500 mg, powder for solution for injection or infusion
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19 January 2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/05/328/001-004

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Cubicin, 350 mg and 500 mg, powder for solution for injection or infusion
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19 January 2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/05/328/001-004

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Cubicin, 350 mg and 500 mg, powder for solution for injection or infusion
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19 January 2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/05/328/001-004
- Bioavailability study number(s): Not applicable

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Kolbeinn Gudmundsson.

- The application was received by the EMA on 8 February 2016.
- The procedure started on 25 February 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 May 2016.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 May 2016.
- During the meeting on 23 June 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 June 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 9 September 2016.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 October 2016.
- During the PRAC meeting on 27 October 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 10 November 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2016.
- During the meeting on 26 January 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Daptomycin Hospira.

2. Scientific discussion

2.1. Introduction

Daptomycin is cyclic lipopeptide antibiotic, which exhibits bactericidal activity against a number of clinically important antibiotic-resistant gram-positive microorganisms.

The mechanism of action involves binding (in the presence of calcium ions) to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

Extensive clinical trials with daptomycin have been conducted all over the world including Europe. Collectively, these studies have documented the efficacy and safety of daptomycin for various indications. Daptomycin is indicated for the treatment in both adults and paediatric (1 to 17 years of age) patients with cSSTI, in adult patients with right-sided IE due to *S. aureus* and in adult patients with bacteraemia caused by *S. aureus* associated with right-sided IE or with cSSTI.

This centralised procedure is based on Article 10(1), generic application, an application for a medicinal product as defined in Article 10(2)(b) referring to a so-called reference medicinal product with a Marketing authorisation granted in a Member State or in the Community. The active substance daptomycin has been in medicinal use for more than 10 years in the Community. The originator Cubicin from Novartis Europharm Ltd. marketed in the Community is the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for solution for injection/infusion containing 350 mg or 500 mg of daptomycin as active substance.

The other ingredient is sodium hydroxide used for pH adjustment.

The product is available in single use 10 ml type I clear glass vials with grey rubber closure and aluminium cap as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on daptomycin is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of daptomycin is N-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-threo-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine[ε]$_1$-lactone corresponding to the molecular formula $C_{72}H_{101}N_{17}O_{26}$ and has a relative molecular mass of 1620.67 and the following structure:

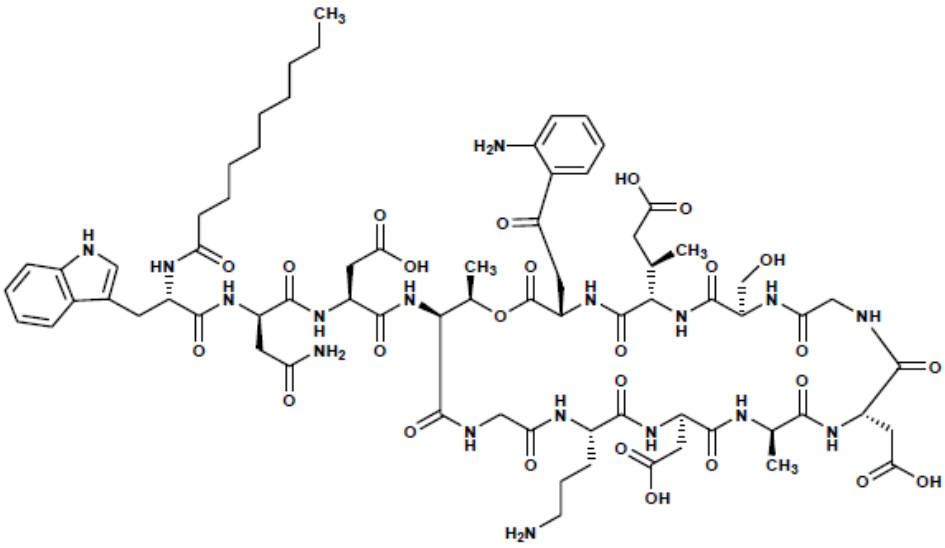

Figure 1. Chemical structure of daptomycin

The structure of the active substance was elucidated by a combination of infrared absorption spectroscopy, UV-VIS absorption spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectroscopy and electrospray ionisation mass spectrometry (ESI-MS). Comparison of IR, UV, NMR and ESI-MS spectra with those of the reference product provided further proof of structure. A screening of crystalline forms was performed using X-Ray Powder Diffraction (XRPD).

The active substance is a pale yellow to yellow, amorphous hygroscopic powder. It is freely soluble in water, slightly soluble in methanol and ethanol and practically insoluble in acetone, ethyl acetate and chloroform. It is sensitive to heat and photosensitive.

Daptomycin exhibits stereoisomerism due to the presence of 13 chiral centres that are controlled in the constituent amino acids and by the fermentation process. Enantiomeric purity is controlled routinely by specific optical rotation. Polymorphism has not been observed for daptomycin and it is only known in the amorphous form. Daptomycin is fully dissolved and lyophilised during finished product manufacturing process, therefore polymorphic form is not considered relevant for finished product performance.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. A single source of the active substance is used.

Daptomycin is manufactured in three main steps: fermentation stage by *Streptomyces roseosporus*, purification stage and lyophilisation stage.

A series of purification steps are carried out to remove impurities and ensure the purity of the active substance. Stereochemistry originates in the raw material inputs and is controlled by the organism during fermentation.

Steps critical to the quality of the active substance have been identified and they are controlled with adequate in-process controls applied during the manufacturing process. The specifications and control methods for intermediate products, starting materials and reagents have been presented and considered as satisfactory. Reprocessing steps and criteria have been defined and considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Adequate purge of reagents and their by-products has been demonstrated.

The active substance is packaged in 2-ply heat-sealed polyethylene bags under vacuum. It is then packaged in heat-sealed aluminium foil bag and placed in an aluminium container. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description (appearance), identification (IR, HPLC), specific optical rotation (USP), clarity of solution (Ph. Eur.), colour of solution (Ph. Eur.), residue on ignition (Ph. Eur.), water content (Ph. Eur.), heavy metals (USP), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur., USP) and microbial limits (Ph. Eur, USP).

Impurities present at higher than the qualification threshold according to ICH Q3A were accepted based on levels found in the originator product, which are considered as qualified. The comparison provided by the Applicant included results of analyses of multiple batches of the originator product, which were sourced from the European market and were tested prior and close to expiry date.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the active substance and impurities has been presented.

Batch analysis data on four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5 °C ± 3 °C) (5 batches) and for up to 6 months under accelerated conditions at 25 °C ± 2 °C / 60% RH ± 5% RH (6 batches) according to the ICH guidelines were provided.

The following parameters were tested: appearance, appearance of solution, pH, water content, specific optical rotation, assay, related substances, residual solvents, bacterial endotoxins and bioburden. The analytical methods used were the same as for release and were stability indicating.

A slight decrease in assay, combined with an increase in total impurities was observed under both long term and accelerated conditions. The increase in total impurities is mainly attributed to the gradual increase of the anhydro daptomycin impurity upon storage. Nevertheless, both the assay and total impurities remained within the specifications under both storage conditions. Other parameters remained constant upon storage under both storage conditions.

Forced degradation studies including acid and base hydrolysis, oxidation, thermal degradation and photolysis in line with ICH Q1B guideline were also performed, indicating that daptomycin was unstable under all conditions tested. The results from this study demonstrated that the proposed methods for assay and related substances are stability indicating and suitable for their intended use, and that the active substance should be stored protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored at proposed conditions in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a sterile powder for solution for injection/infusion containing 350 mg or 500 mg of daptomycin as active substance per vial. The product is intended for reconstitution with sodium chloride 0.9% solution for injection prior to intravenous administration. The aim of the pharmaceutical development was to develop a finished product equivalent to that of the reference medicinal product, Cubicin.

The only excipient present in the finished product is sodium hydroxide used for pH adjustment of the bulk formulation. According to the information provided, water for injection is a co-solvent/vehicle which is removed from the final product by lyophilisation. Nitrogen is a processing agent used during the manufacture (following lyophilisation and during stoppering steps) as air displacement to minimise the moisture content in the vials. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. Since the excipients selected are the same used for the reference medicinal product, no excipient compatibility studies were performed.

During pharmaceutical development a number of comparative studies were performed that demonstrated that Daptomycin Hospira is comparable to the reference product. The following quality attributes were investigated: identity, physico-chemical properties, related substances profile, biological activity and stability. Both products are nearly identical for all tested quality attributes. Both products have the same osmolality. As mentioned earlier in the report, the active substance is freely soluble in aqueous media but it is photosensitive and sensitive to heat. Photostability studies were conducted to assess the worst case impact of this condition on the product during the manufacturing process. No significant differences between the exposed sample and the control were observed under these conditions. The finished product is lyophilised and not photosensitive as confirmed by the photostability study conducted in line with ICH Guideline on Photostability Testing of New Drug Substances and Products (see stability section).

Hold time studies were performed on bulk solution. Stability of the bulk solution was confirmed and acceptable maximum holding times were defined.

The finished product is manufactured using a non-standard process as it is aseptically processed. Selection of the sterilization method was appropriately justified. As the active substance and the finished product are heat

sensitive and other sterilisation methods result in significant increase in impurity levels, an aseptic filtration/filling process of the product was selected.

The primary packaging is single use 10 ml type I clear glass vials with grey rubber closure and aluminium cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. A compatibility study with 0.9% sodium chloride (the proposed reconstitution solution) and the container closure system was also performed. The results demonstrated that Daptomycin Hospira solutions are stable under tested conditions and comparable to the reference product. A study of the extractables and leachables that could be present in the reconstituted finished product demonstrated that no significant extraction or leaching occurred.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: dispensing, compounding, sterile filtration (passed through two 0.2 µm filters in series), aseptic filling and lyophilisation. The processing steps and parameters that were considered critical to the finished product quality include the active substance handling, bulk solution pH and temperature, aseptic filtration and filling, and lyophilisation. The process is considered to be a non-standard manufacturing process.

A detailed description of the manufacturing process of the finished product including the manufacture of the bulk solution, subsequent steps of the sterile filtration and respective in-process controls has been provided. Appropriate in-process controls were used during the manufacturing process of the finished product.

Major steps of the manufacturing process have been validated by a number of studies. Validation data was provided and considered acceptable. The formulation and manufacturing process for all presentations of the finished product are identical with the exception of the final fill volume. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for a sterile parenteral dosage form and include: description (visual), description of solution (visual), identification (IR, HPLC), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), water content (Ph. Eur.), reconstitution time (visual), particulate matter (Ph. Eur.), uniformity of dosage units (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches of each strength of the finished product stored under long term conditions for 36 months at 5 °C ± 3 °C, intermediate conditions for 6 months at 15 °C ± 2 °C and for 6 months under accelerated conditions at 25 °C ± 2 °C / 60% RH ± 5% RH were provided. The batches of medicinal

product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, supportive stability data on four batches (3 batches for 350 mg/vial strength and 1 batch for 500 mg/vial presentation) intended for the marketing authorisation application in the US were provided. Testing was conducted under long term conditions for up to 36 months at 5 °C ± 3 °C and for 6 months under accelerated conditions at 25 °C ± 2 °C / 60% RH ± 5% RH. These batches were representative of the batches intended for the EU market and the analytical methods used are the same as those applied for in this application.

Samples were tested for description, description of solution, pH, assay, related substances, water content, reconstitution time (visual), particulate matter, sterility and bacterial endotoxins. The analytical procedures used are the same as the methods used for release testing and they are stability indicating. The vials were stored in upright and inverted positions.

All results of the stability study complied with the proposed shelf-life specification.

Stress studies on the finished product were performed by storing the product in a freezer (-15 °C to -25°C) for 1 month. Results showed that the freeze-thaw conditions had no impact on the finished product since all attributes (appearance, pH, assay, related substances and water content) remained unchanged.

Forced degradation studies on one lab scale batch exposed to acid, base, heat, oxidation (H_2O_2) and light were also conducted. The data demonstrates that the product is susceptible to degradation under all these conditions, and especially under heat and alkali conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No signs of degradation after exposure to light were observed. Therefore, the finished product is not considered to be photosensitive.

As indicated under pharmaceutical development, since Daptomycin Hospira is required to be reconstituted with 0.9% sodium chloride prior to administration, a study to demonstrate the stability of the product upon reconstitution and storage for up to 12 hours at room temperature or up to 48 hours under refrigeration at 2 °C to 8 °C, was conducted. The results demonstrated that similarly to the reference medicinal product, the reconstituted product is stable when reconstituted as described in the product information.

Based on available stability data, the proposed shelf-life of 3 years when stored in a refrigerator (2 °C – 8 °C) as stated in the SmPC (section 6.3) is acceptable. 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; see section 6.6) 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 (see section 6.6) at 25°C must not exceed 12 hours (or 48 hours 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.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Development of the generic product was based on the formulation, dosage form, concentration and use of the reference product. The composition of the generic formulation is qualitatively identical and quantitatively nearly identical to the innovator product Cubicin. The active substance is manufactured using classical fermentation from *Streptomyces roseosporus.* It is formulated with a single excipient, sodium hydroxide (for pH adjustment), and presented as 350 mg or 500 mg sterile powder for solution for injection/infusion.

Comparative experimental data regarding the physicochemical characteristics, e.g. identity, physico-chemical properties, related substances profile, biological activity and stability have been provided. No significant differences were observed from the comparative studies between the generic product and the reference product. Therefore, similarity between Daptomycin Hospira and the reference product Cubicin can be accepted.

The finished product is manufactured using a non-standard manufacturing process, as it consists of sterile filtration and aseptic processing. Based on the provided process validation data, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Daptomycin Hospira manufactured by Hospira UK Ltd. is considered unlikely to result in any significant increase

in the combined sales volumes for all daptomycin containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

An environmental risk assessment is not required.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Daptomycin Hospira from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Daptomycin Hospira and the reference product Cubicin, proprietary medicinal product with central marketing authorisation [EMEA/H/C/000637(II-0053)] have an identical SmPC.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

2.4.2. Pharmacokinetics

No bioequivalence study was submitted to support the application and no study is required according to Appendix II to the Guideline on the Investigation of Bioequivalence as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. The test product contains the same excipient as the reference product.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The application contains an adequate review of published clinical data. No bioequivalence study is required for this application according to Appendix II of the Guideline on the Investigation of Bioequivalence.

Daptomycin Hospira is essentially similar to the reference product Cubicin of Novartis Europharm Limited.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Daptomycin Hospira and justifications that the product

is essentially similar in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Severe skeletal muscle toxicity • Reduced susceptibility to daptomycin in *S. aureus* • Peripheral neuropathy • Severe hypersensitivity reactions (including pulmonary eosinophilia) • Eosinophilic pneumonia • Acute generalised exanthematous pustulosis (AGEP)
Important potential risks	• Bone marrow toxicity • Severe hepatotoxicity • Dysregulation of *in vivo* coagulation
Missing information	• Patients with underlying renal impairment • Patients with hepatic impairment • Pregnant or lactating women

Pharmacovigilance plan

There are no on-going and planned studies in the post-authorisation pharmacovigilance development Plan for daptomycin Hospira.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Severe skeletal muscle toxicity	Text in SmPC as detailed under Section 4.4 “Special warnings and precautions for use”; Section 4.5 “Interaction with other medicinal products and other forms of interaction”; Section 4.8 “Undesirable effects”; and Section 5.3 “Preclinical safety data”. Text in PIL as stated under Section 2 “What you need to know before you use daptomycin Hospira”; and Section 4 “Possible side effects”.	Dosage card
Reduced susceptibility to daptomycin in *S. aureus*	Text in SmPC as detailed under Section 4.4 “Special warnings and precautions for use”; Section 5.1 “Pharmacodynamic properties”.	The laboratory susceptibility testing leaflet
Peripheral neuropathy	Text in SmPC as detailed under Section 4.2 “Posology and method of administration”; and Section 4.4 “Special warnings and precautions for use”; Section 4.8 “Undesirable effects”; and Section 5.3 “Preclinical safety data”.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Text in PIL as stated under Section 2 “What you need to know before you use daptomycin Hospira”; and Section 4 “Possible side effects”.	
Severe hypersensitivity reactions (including pulmonary eosinophilia)	Text in SmPC Section 4.3 “Contraindications”; Section 4.4 “Special warnings and precautions for use”; and Section 4.8 “Undesirable effects”. Text in PIL as stated under Section 2 “What you need to know before you use Daptomycin Hospira”; and Section 4 “Possible side effects”.	None
Eosinophilic pneumonia	Text in SmPC as detailed under Section 4.4 “Special warnings and precautions for use”; and Section 4.8 “Undesirable effects”. Text in PIL as stated under Section 2 “What you need to know before you use daptomycin Hospira”; and Section 4 “Possible side effects”.	None
Acute generalised exanthematous pustulosis (AGEP)	Proposed text in SmPC as detailed under Section 4.8 “Undesirable effects”.	None
Bone marrow toxicity	Text in SmPC as detailed under Section 4.8 “Undesirable effects”. Text in PIL as stated under Section 4 “Possible side effects”.	None
Severe hepatotoxicity	Text in SmPC as detailed under Section 4.2 “Posology and method of administration”; Section 4.8 “Undesirable effects”; and Section 5.2 “Pharmacokinetic properties”.	None
Dysregulation of *in vivo* coagulation	Text in SmPC text as detailed under Section 4.4 “Special warnings and precautions for use”; Section 4.5 “Interaction with other medicinal products and other forms of interaction”; and Section 4.8 “Undesirable effects”. Text in PIL as stated under Section 2 “What you need to know before you use daptomycin Hospira”.	Dosage card
Patients with underlying renal impairment	Text in SmPC as detailed under Section 4.2 “Posology and method of administration”; Section 4.4 “Special warnings and precautions for use”; Section 4.5 “Interaction with other medicinal products and other forms of interaction”; Section 4.8 “Undesirable effects”; and Section 5.2 “Pharmacokinetic properties”. Text in PIL as stated under Section 2 “What you need to know before you use daptomycin Hospira”; Section 3 “How to use daptomycin Hospira”; and “Section 4 “Possible side effects”.	None
Patients with hepatic impairment	Text in SmPC as detailed under Section 4.2 “Posology and method of administration”; Section 4.8 “Undesirable effects”; Section 5.2 “Pharmacokinetic properties”.	None
Pregnant or lactating	Text in SmPC as detailed under Section 4.6 “Fertility, pregnancy	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
women	and lactation"; and Section 5.3 "Preclinical safety data". Text in PIL as stated under Section 2 "What you need to know before you use daptomycin Hospira".	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of daptomycin. The reference product Cubicin is indicated for the treatment in both adults and paediatric (1 to 17 years of age) patients with complicated skin and soft tissue infections (cSSTI), in adult patients with right-sided infective endocarditis (IE) due to *S. aureus* and in adult patients with bacteraemia caused by *S. aureus* associated with right-sided IE or with cSSTI. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference

medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Daptomycin Hospira is favourable in the following indication:

Daptomycin is indicated for the treatment of the following infections (see sections 4.4 and 5.1).

- 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. (see sections 4.4 and 5.1).
- Adult patients with *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI.

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

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe/use Daptomycin Hospira 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 CPK at treatment initiation and at regular intervals is important. Patients at higher risk of developing myopathy should have more frequent CPK measurements.
- That Daptomycin Hospira can interfere with coagulation tests (PT/INR) 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 Hospira trough plasma concentration.
- The dosage card should contain the appropriate algorithms for calculating the Daptomycin Hospira dose for reconstitution, to help minimise the risk of medication errors (high osmolarity, overdose).

The Marketing Authorisation Holder shall ensure that all laboratories expected to perform Daptomycin Hospira 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 Ca in the testing medium and testing methods with mediums providing consistent Ca concentrations are recommended.