1. Introduction

The majority of skin and soft tissues infections (SSTIs) are caused by usually *Staphylococcus aureus* or β-haemolytic streptococci. SSTIs are considered complicated when they involve deeper skin structures, such as fascia or muscle layers, require significant surgical intervention or arise in the presence of significant co-morbidity.

The inexorable increase in the prevalence of bacterial resistance since the 1940s now threatens the utility of some antibiotics for treating certain species. Infections due to Gram-positive bacterial species are now the foremost problems in many specialised units and institutions. Methicillin-resistant *S. aureus* (MRSA), glycopeptide-insusceptible *S. aureus* (GISA) and glycopeptide-resistant enterococci (VRE or GRE), particularly *E. faecium*, are of particular concern. For example, the European Antimicrobial Resistance Surveillance System (EARSS) study of 2002 reported that 22% of *S. aureus* isolates were methicillin-resistant overall, with the highest rates recorded in participating centres in Greece (44%), Ireland (42%), Malta (43%) and the UK (44%). The highest rates of vancomycin-resistant *E. faecium* were reported from Greece (19%), Italy (21%) and Croatia (22%). Bulgaria, Greece and Hungary reported the highest prevalence of high-level aminoglycoside-resistant *E. faecalis*. Other gram-positive species, such as coagulase-negative staphylococci and *Corynebacteria spp*., have also caused problems due to acquisition of multiple resistance determinants.

Therefore, there is a need for additional agents that might be clinically active against these difficult to treat pathogens to the existing antibiotic armamentarium.

The present application for marketing authorisation of CUBICIN (350 or 500 mg powder for concentrate for solution for infusion) is made under Article 8.3 (i) and concerns a new active substance, daptomycin.

Daptomycin is a novel cyclic lipopeptide derived from a natural product of *Streptomyces roseosporus*.

The approved indication at the recommended dose of 4 mg/kg administered as a single daily dose for 7-14 days or until the infection is resolved is: CUBICIN is indicated for the treatment of complicated skin and soft-tissue infections in adults (see sections 4.4 and 5.1 *of the Summary of Product Characteristics*).
Daptomycin is active against Gram-positive bacteria only (see section 5.1 *of the Summary of Product Characteristics*). In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, CUBICIN should be co-administered with appropriate antibacterial agent(s).

2. Quality aspects

Introduction

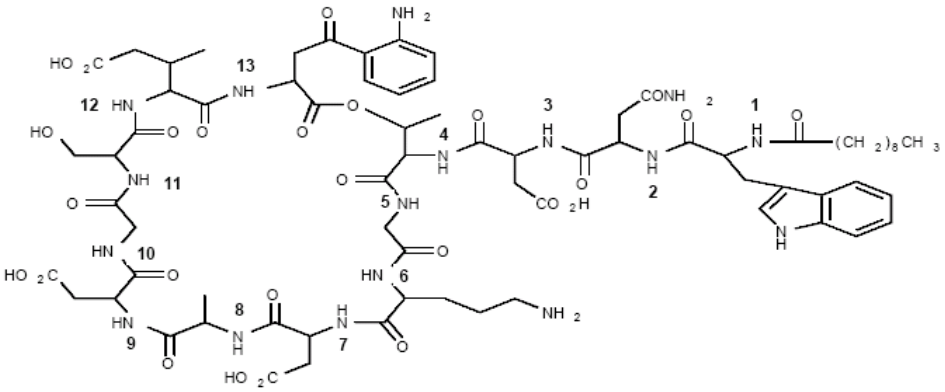
CUBICIN is formulated as a single use powder for concentrate for solution for infusion containing 350 mg or 500 mg of daptomycin, as active substance. Following reconstitution with 9 mg/ml (0.9%) sodium chloride for injection or water for injections (7 ml for the 350 mg strength and 10 ml for the 500 mg strength) to yield to a 50 mg/ml solution, the product is administered by intravenous infusion after dilution in sodium chloride 9 mg/ml (0.9%).

The other ingredients include sodium hydroxide.

It is presented in 10 ml glass vials closed with a rubber stopper, an aluminium seal and a plastic flip-off cap.

Drug Substance

Daptomycin is a novel macrocyclic peptide, with a decanoyl side chain linked to the N-terminus Tryptophan, produced by fermentation of *Streptomyces roseosporus*.It was selected based on a superior relative therapeutic index in mice from a 6-lipopeptide antibiotic complex in which each peptide has the same inactive 13 amino acid nucleus with various fatty acid acyl groups on the N-terminus. Detailed information on quality/control of materials used in the fermentation process and subsequent purification steps, has been provided by the way of an active substance master file.



Residues		
	1 Trp	8 Ala
	2 Asn	9 Asp
	3 Asp	10 Gly
	4 Thr	11 Ser
	5 Gly	12 3-MeGlu
	6 Orn	13 Kyn
	7 Asp	

The frozen active substance yields a clear, dark yellow to light brown solution upon thawing. X-ray diffraction studies indicated that daptomycin powder is amorphous. It is highly soluble in water.. Stress stability studies showed that it degradates when exposed to direct light, heat, oxygen and to extreme pHs in solution.

- Manufacture

Daptomycin is produced by 2 different manufacturers. The manufacturing process includes the following steps: fermentation (inoculum preparation, fermentation and harvest), purification by chromatography and ultrafiltration, and filling in low-density polyethylene (LDPE) bioprocess container. Critical process parameters have been identified and respective process ranges and/or set points have been satisfactorily established.
Characterisation of impurities has been conducted based on detailed evaluation of daptomycin impurity profile. The main impurities include 3 fermentation process related impurities and three degradation products namely anhydro-daptomycin, ß-aspartyl isomer and lactone hydrolysis product of daptomycin. The only solvent used during synthesis is a class 3 solvent.

During development, the active substance was obtained from 3 different manufacturers. Changes were made to the purification steps and to the final presentation of daptomycin (frozen concentrate instead of lyophilised powder). Comparative analytical results demonstrate that daptomycin batches used in pre-clinical and clinical studies produced according to the current and the earlier processes are physicochemically equivalent.

- Specification

The active substance specification includes tests for appearance, identity (UV and FTIR), assay (HPLC), impurity content (HPLC), residual solvents (GC), pH, bacterial endotoxins, microbial limits, specific rotation, heavy metals and residue on ignition.
The impurity limits have been satisfactorily justified based on toxicology studies.

Batch analysis data provided for 5 consecutive commercial batches manufactured at one site and for 3 consecutive batches manufactured at the other site confirm satisfactory compliance and uniformity with the proposed specifications.

- Stability

Stability data have been provided for 3 batches manufactured by both manufacturers. 6-month data are available under accelerated conditions (5ºC±3ºC – scale down commercial packaging) and up to 2-year data are available under long-term conditions (-20ºC±5ºC – scale down commercial packaging). Samples were tested for appearance, assay, pH, and impurities.
Data in support of the stability of the active substance when raised briefly to higher temperatures, as might be experienced during transit, were also satisfactory. Stress testing included photostability, pH stability profile, thermal degradation and oxidative degradation. 2 batches have been satisfactory studied for potential extractables and leachables following storage at -20ºC for up to 20 months.
The proposed retest period is supported by the presented data when daptomycin is stored in a LDPE bioprocess container stored in a sealed plastic bag placed in a foil outer bag.

Drug Product

- Pharmaceutical Development

The degradation profile of daptomycin was the main parameter to take into account during the pharmaceutical development (see active substance).

The target in-process pH range (4.5-5.0) was selected based on the sensitivity of the active to extreme pHs. Given the high solubility of the active, the only excipients considered necessary were the vehicle, sodium hydroxide to achieve the target pH and nitrogen as process aid during lyophilisation. Sodium citrate and mannitol used as bulking agents for the formulation of early batches became unnecessary as the dose for clinical use increased. All the excipients are of PhEur quality. Regarding the TSE risk, CUBICIN does not contain any component of ruminant origin.
The 5% daptomycin overfill is suitable to allow the label claim volume to be withdrawn from the vial after reconstitution.

The container closure system, consisting of a type I glass vial closed by a rubber stopper capped with an aluminium seal and a flip-off plastic cap, meet the PhEur requirements. Integrity of the closure to microbiological and thermal challenges has been demonstrated.

The reconstituted and diluted finished product has been shown to be physically and chemically compatible with sodium chloride for injection 9 mg/ml (0.9%), water for injections used as diluents and with some of the commonly intravenously administered medications (see section 6.6 of the SPC). Possible sorption of daptomycin on tubes and bags used during intravenous infusion has been satisfactorily investigated.

In order to minimise potential daptomycin degradation during the manufacturing process, refrigerating conditions are used, lyophilisation is performed under nitrogen atmosphere and a prefiltration step was introduced prior to pooling of the bulk substance in order to reduce the processing time during sterile filtration process. The choice of sterilisation by filtration is justified by the peptidic nature of daptomycin and its sensitivity to heat.

Slightly different formulations (including sodium citrate or mannitol used as bulking agents) and diluents have been used in early clinical studies. This is not expected to have any impact on the product performance based on the type of molecule and the mode of administration.

- Manufacture of the Product

CUBICIN is produced at two different sites. The method of manufacture involves the following operations designed to minimize any potential degradation of the active (see pharmaceutical development): thawing of the active substance, pre-filtration, pooling, pH and concentration adjustment, sterile filtration, filling, lyophilisation and packaging.
Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Holding times and conditions for the pooled active substance before dilution and for the formulated product before filling have been adequately justified based on validation data.
Satisfactory validation data have been provided on production scale batches for the relevant strengths at both manufacturing sites.

- Product Specification

The finished product specification include tests for appearance, identification (UV and FTIR), pH, assay (HPLC), powder fill weight, degradation products, uniformity of content (PhEur), water content (PhEur), bacterial endotoxins (PhEur), particulate contamination (PhEur), sterility (PhEur), container closure integrity and reconstitution time.
The degradation products limits have been satisfactorily justified based on toxicology studies.
Satisfactory batch analysis data have been provided for full-scale batches manufactured at both sites.

- Stability of the Product

- Before reconstitution and dilution

Stability data are presented for 3 batches of each strength (250 mg/vial and 500 mg/vial). 3-year data under long term conditions (5ºC - proposed packaging) and under accelerated conditions (25ºC/60%RH - proposed packaging) have been provided.
The parameters tested included appearance, assay, related substances, pH of reconstituted solution, water content, particulate contamination and container closure integrity. Photostability investigated in line with ICH recommendations showed that the product is not sensitive to light when stored in its original packaging.

- After reconstitution

Chemical and physical in-use stability of finished product has been examined after reconstitution with 9 mg/ml (0.9%) sodium chloride for injection or water for injections. The reconstitution time is typically 15 minutes, which is rather long. This is specified in the Summary of Product Characteristics.

- After reconstitution and dilution

Chemical and physical in-use stability of the reconstituted finished product diluted in normal saline infusion bags has been studied.

The results presented support the proposed shelf life and storage conditions defined in the Summary of Product Characteristics for the finished product before reconstitution and dilution, after reconstitution, and after reconstitution and dilution.

3. Non-clinical aspects

Introduction

The development of daptomycin began in the early 1980s but was terminated due to observations of adverse skeletal muscle effects in animals, and in a low number of subjects, during Phase 1 clinical trials. In the late 90's Cubist licensed daptomycin from Lilly in 1997, the non-clinical and clinical development of daptomycin resumed.
The development programme spans some 20 years, some studies were conducted prior to the issuance of CHMP/ICH guidelines. Nonetheless, the non-clinical studies were appropriately and adequately conducted for the state of the science of the day. Although the bulk of the toxicological assessment of daptomycin was performed in rats and dogs, primates were used in a single and a repeat dose study. All the pivotal *in vivo* toxicity studies (with the exception of genotoxicity) were conducted using the *iv* route of administration, the intended route of clinical administration. All of the pivotal repeat dose toxicity studies were conducted in compliance with Good Laboratory Practices (GLP) regulations. The lack of GLP compliance for selected acute toxicity and investigative studies as well as some toxicokinetic studies is not considered to have invalidated them.

Pharmacology

The primary pharmacology studies focused on *in vitro* microbiological profiling, animal models of infection, and pharmacodynamic studies correlating efficacy with pharmacokinetic parameters. Secondary and safety pharmacology studies were also performed.

- Primary pharmacodynamics

Daptomycin is a novel cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*.

Daptomycin inserts directly into the cytoplasmic membrane of Gram-positive cells (aerobes and anaerobes). This action is calcium-dependent and results in a rapid depolarisation of the membrane, thus giving rise to the efflux of potassium ions. Bacterial DNA, RNA and protein synthesis is rapidly stopped with subsequent cell death that does not depend upon lysis. The antibacterial activity of daptomycin requires the presence of free calcium. The exact mechanism of action of daptomycin remains to be determined.

Due to its different mechanism of action, the antibacterial activity of daptomycin is not affected by mechanisms that confer specific resistance to beta-lactam agents (including methicillin), glycopeptides (such as vancomycin), quinupristin/dalfopristin, linezolid or other agents potentially useful against Gram-positive bacterial species.

In both *in vitro* and *in vivo* studies, the action of daptomycin was bactericidal against a number of clinically important antibiotic-resistant Gram-positive bacteria including *Staphylococcus* spp. (including both methicillin- and vancomycin-resistant isolates), *Enterococcus* spp. (including vancomycin-resistant isolates), and *Streptococcus* spp. (including penicillin-resistant isolates).
Further information can be found in the clinical part under the pharmacodynamics section.

Daptomycin had poor *in vitro* activity against both aerobic and anaerobic Gram-negative organisms.

- Safety pharmacology

Safety pharmacology was primarily investigated in rodents, dogs, and *in vitro* models. No adverse effects on the cardiovascular, respiratory, renal, gastrointestinal or immune systems were observed *in vivo* at clinically relevant doses.

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