SCIENTIFIC DISCUSSION

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

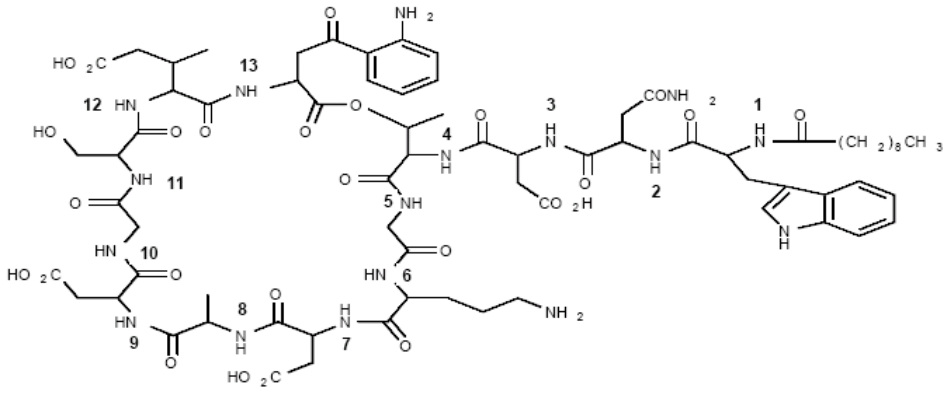
CUBICIN is formulated as a single use powder for concentrate for solution for infusion containing 350 mg or 500 mg of daptomycin, as active substance. Following reconstitution with 9 mg/ml (0.9%) sodium chloride for injection or water for injections (7 ml for the 350 mg strength and 10 ml for the 500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

Daptomycin's effects on the central nervous system as well as the neuromuscular system were assessed in a series of in vivo and in vitro studies. Effects on the nervous and/or muscular system were evident at high dose *iv* levels in rodents (≥ 50 mg/kg). Depressive clinical signs included abnormal gait and/or posture, and decreased motor activity and motor coordination.
Marked effects on the central nervous system in animals were observed only at *iv* dose levels of ≥ 150 mg/kg. At doses ≥ 200 mg/kg in mice, tremors and clonic convulsions were observed; with death occurring at ≥ 1000 mg/kg. No corresponding effects were observed in rats at 150 mg/kg.

No effect on EEG or neuromuscular conduction was noted in dogs after acute administration of daptomycin at *iv* dose levels of 50 and 30 mg/kg, respectively.

Daptomycin appears to have no clinically relevant pharmacological activity in cardiac or smooth muscle. *In vitro,* at high concentrations (up to 25-fold peak plasma concentration observed in patients at intended clinical dose of 4 mg/kg/day), no effects were seen in cardiac (atria) or smooth muscle preparations (ileum, jejunum, or aorta). Effects were limited to selective antagonism of rat uterus and vas deferens smooth muscle preparations. However, the concentration at which these effects were observed (160 µg/ml free drug) is 30-fold greater than the maximal concentration of free drug in patients at the intended clinical dose of 4 mg/kg/day.

There was no potential for prolongation of QT interval based on exposure of the hERG channel up to 100 times the clinical plasma concentrations.

- Pharmacodynamic drug interactions

Use of daptomycin in combination therapy was investigated in a number of animal models of infection. These studies showed synergistic increases in efficacy with amikacin, tobramycin, gentamicin and rifampicin.

Pharmacokinetics

Single and multiple dose pharmacokinetics studies were conducted in mice, rats, beagle dogs, and rhesus monkeys using both unlabelled and radiolabelled daptomycin. As the intended clinical route is intravenous, the majority of the studies used this route of administration. Toxicokinetic studies were included in the 6-month rat study (Day 1 only) and in all repeat-dose studies in dogs (up to 6-months) and in monkeys (1-month).
Published literature on daptomycin provided supportive data, as well as information on pharmacokinetics in other species, such as rabbits and guinea pigs, and information on serum protein binding. Methods of analysis were adequate.

- Absorption- Bioavailability

Overall, the pharmacokinetic characteristics were generally comparable across the 4 species tested.

Studies in rats showed that daptomycin was poorly absorbed orally and exhibited slow passage through the gastrointestinal tract with > 90% excreted in the faeces.

Limited data indicated a relatively high bioavailability after s.c. or i.p. administration. Daptomycin plasma profile following *iv* injection was consistent with a 2-compartement model with a rapid distribution phase and slower elimination phase.
Daptomycin exhibited linear kinetics following intravenous injection across a dose range of 1 to 50 mg/kg in the rat, 1 to 200 mg/kg in the dog, and 1 to 25 mg/kg in the monkey.

For all species, plasma clearance, volume of distribution, and terminal half-life were dose-independent over the linear range. Within the linear range, terminal half life of daptomycin was 1 – 3 hours in rodents and 2 – 4 hours in non-rodents. The pharmacokinetic profile of daptomycin was similar between strain and gender and was not altered upon repeated daily administration for up to 6 months.

- Distribution

In the rat, the only species in which tissue distribution was studied, daptomycin distributes rapidly from the plasma to the tissues with a distribution phase half-life (t½ α) of approximately 7 minutes. The volume of distribution was essentially the same (approximately 60 to 160 ml/kg) in mice, rats, dogs, monkeys and humans, and clearance scales to body size. Daptomycin appears to distribute preferentially to the kidneys, reflecting the vascularisation of the tissue as well as renal concentration of the drug during excretion. Daptomycin is shown cross the placenta in pregnant rats and to enter the CNS, but data suggest that no extensive penetration across the blood-brain or placental barriers appear to occur. .

In general, the half-life in tissues was slightly greater than that in plasma and tissue levels were higher after repeated dosing than after a single dose. No accumulation was observed in plasma upon repeated administration in rats, dogs, or monkeys.

There is no data on the excretion of daptomycin into milk. Therefore,
breastfeeding should be discontinued during treatment as indicated in the Summary of Product Characteristics.

Published data indicated that the extent of protein binding was the same in mice, rabbits and humans (approximately 90%). Although direct measurements were lacking in rats, dogs and monkeys, pharmacokinetic data suggested that the extent of protein binding was consistent among species.

- Metabolism (*in vitro/in vivo*)

In vivo metabolism studies performed in mice, rats, dogs and monkeys showed that daptomycin exhibited limited metabolism. Although the studies were not up to the current standard, pharmacokinetics data showed that daptomycin was primarily eliminated in animals as intact in the urine confirming that it undergoes little or no systemic metabolism. PK studies indicated that it did not appear to inhibit or induce any of the key cytochrome P450 isoenzymes. Therefore, the potential for metabolic drug-drug interactions should be limited and the potential for pharmacokinetic drug interactions with daptomycin is probably low.

- Excretion

Daptomycin was excreted primarily *via* the kidney largely as unchanged. In mice, rats, dogs, monkeys most of the compound (≥ 70 %) was recovered in the urinary within 48 hours post-dose. Faecal excretion accounted for approximately 3 to 10 % of the administered radioactivity in these species. This is comparable to the human data. In rats less than 2 % of the administered radioactivity was recovered in the expired air.

A study in juvenile dogs showed that total systemic clearance appears to be faster in juvenile dogs as compared to adults, resulting in shorter terminal half-life and lower $AUC_{0\text{-}24}$, at the same dose level.

In rats with renal impairment, the systemic clearance was reduced by ~70 % compared to that of normal rats. This resulted in a ~1.5 to 2-fold increase in peak plasma concentration (T_{max}), a 2 to 3-fold increase in the AUC, and increased half-life. Volume of distribution was decreased by 53 %.

Toxicology

- Single dose toxicity

After single dose *iv* bolus injection of daptomycin, clinical signs suggestive of toxicity to the skeletal muscle and/or nervous systems (CNS and peripheral nerves) were evident in all 4 species (mouse, rat, dog and monkey) and were accompanied by decreases in body weight and/or body weight gain in rodents and dogs. Mortality occurred across animal species at dose levels 25 to >100 fold higher than the clinical dose of 4 mg/kg. In mice, there were no significant toxicity signs after single oral administration up to 2000 mg/kg. Sc administration of daptomycin to rats was less toxic than *iv* injection. The peak plasma levels of daptomycin in animals at the minimal lethal dose ranged from approximately 30 to 100 times that at the intended clinical dose. Primates appeared to be the most sensitive animal species.

- Repeat dose toxicity (with toxicokinetics)

The repeat dose toxicity has been studied in rats and dogs up to 6 months, and monkeys up to 1 month. Daptomycin was administered by bolus *iv* injection in all studies, with one study also investigating administration *via* 30 minute *iv* infusion. For most studies, daptomycin was administered once daily, except for select investigative studies in which it was also administered every 8 hours. The main finding are displayed in Table 1.

Table 1:

Species/strain	**Study duration**	**Dose range (mg/kg/day)**	**Signs of toxicity identified**
Rat Fischer	1 month	25-150	Skeletal myopathy, renal effects, peripheral neuropathy (high dose)
Rat Fischer	1 month	10-20	Skeletal myopathy, renal effects.
Rat Fischer	3 months	1-20	Skeletal myopathy.
Rat Fischer	3 months	5-80	Skeletal myopathy, renal effects, bone marrow.
Rat Fischer	6 months	2-50	Skeletal myopathy, bone marrow.
Dog Beagle	2 weeks	25-100	Skeletal myopathy, nerve.
Dog Beagle	1 month	10-75	Skeletal myopathy, peripheral neuropathy (high dose), bone marrow.
Dog Beagle	6 months	2-40	Skeletal myopathy, nerve, bone marrow.
Monkey Rhesus	1 month	1-10	No evidence of skeletal myopathy, peripheral neuropathy or renal changes

The results of the repeat dose and investigative studies consistently demonstrated daptomycin's primary target organ to be skeletal muscle in rats and dogs, with effects observed in peripheral nerve at higher dose levels in both species.

Skeletal muscle

Daptomycin-induced myopathy was specific to the skeletal muscle in the rat and dog, which occurred at exposure levels below human therapeutic levels. No functional or pathological changes were observed in cardiac or smooth muscle.
Microscopic changes to skeletal muscles were typically characterised by minimal to mild degeneration with regeneration. Degeneration was confined to a few (single, randomly distributed) myofibres. Under light microscopy, degeneration was generally characterised by myofibre swelling, sarcoplasmic hyalinization or vacuolation, fragmentation and/or loss of cross striations, accompanied by inflammatory infiltrates. Electron microscopic examination of slightly degenerative fibres revealed streaming of the Z-band and, in more affected fibres, disorganisation and loss of myofilaments and minimal myofibril lysis, occasionally associated with mitochondria swelling and aggregation. In the degenerative fibres, there was no evidence of disruption of cristae or calcium deposits in the mitochondria. All muscle effects, including microscopic changes, were reversible within 3 months following cessation of dosing.
No evidence of rhabdomyolysis was observed even at the highest dose levels tested in non-clinical studies.

The degrees of skeletal myopathy appeared to be related to the dosing frequency and AUC, and were usually accompanied by elevations in creatinine phosphokinase (CPK). It was hypothesised that once-daily administration reduced the potential for skeletal myopathy because this dose regimen results in more time at low plasma concentrations and, consequently, greater time between doses for repair of the affected myofibres. Dog studies have demonstrated that serum daptomycin levels below 10 µg/ml were not associated with cumulative skeletal muscle damage.

Although the precise mechanism of daptomycin's effect on skeletal muscle has not been completely elucidated several possible mechanisms were ruled out based on comparisons with other myotoxic drugs. Daptomycin-induced myopathy did not appear to share the characteristics associated with inflammatory myopathy or rhabdomyolysis, and the muscle damage is unlikely to be mediated through a direct effect on calcium flux and/or channels. Daptomycin probably causes a direct effect on skeletal muscle rather than an indirect effect through alterations in associated tissue(s). Daptomycin had no effect on the contractility of vascular tissue, which could lead to ischemia-reperfusion of the muscle fibres. Daptomycin-related myopathy was observed at dose levels that are not associated with peripheral neuropathy, indicating that the mechanism of muscle toxicity is not related to a change in muscle fibre innervation or secondary to the nerve effects.

Peripheral nerves

Daptomycin treatment was also associated with effects on peripheral nerves in adult rats and dogs at doses higher than those associated with skeletal myopathy. Dog was the most sensitive species. In juvenile dogs, degenerative effects in the peripheral nerve and spinal cord were evident at a dose of 50 mg/kg/day, which was a lower dose than those producing muscle lesions (see "Other toxicity studies"). The peripheral neuropathy was characterised by axonal degeneration in the absence of effects on the neuronal cell body; these microscopic lesions were associated with clinical signs (e.g. abnormal posture and gait, as well as impaired coordination, inability to stand, and sternal recumbency) and electrophysiological evidence (e.g. reduction in nerve conduction velocities for both motor and sensory nerves).
Peripheral neuropathy appears to be related to C_{max}. Across the repeat dose studies, the severity of morphologic lesions in the nerve increased with dose but not duration of dose administration. Peripheral nerve effects appeared to be reversible during a 6-months recovery period, consistent with the absence of a microscopic effect on the neuron. The rate of recovery from daptomycin-related nerve effects appears to be dependent upon severity of the effects and, therefore, dose. Assessment of reversibility was, however, limited to studies in dogs. No mechanistic studies have been conducted on the peripheral neuropathy. Non-clinical studies have shown nonetheless that skeletal muscle and peripheral nerves effects are independent (i.e. myopathy not secondary to neuropathy).

Other effects

Mild renal and gastrointestinal effects were observed in rats, but appeared to be species-specific as they were not evident in either dogs or monkeys.
The localisation of daptomycin in the kidney of rats may explain the mild nephrotoxic effects observed in this species. No indication of kidney toxicity was observed in either the dog or the monkey after repeat dose injection, suggesting that renal accumulation of daptomycin either did not occur or was non-toxic in these species.
Signs of bone marrow toxicity (decreased myeloid to erythroid ratio, decreased erythrocyte, reticulocyte, total leukocyte and neutrophil, thrombocyte and monocyte numbers) were observed in both rats and dogs. These changes, although not consistent in pattern, were treatment-related and occurred at low doses (2 mg/kg/day in the rat). The re-examination of these findings suggested that any apparent haematological/bone marrow effects were adaptive as opposed to treatment-related bone marrow toxicity.

Adverse effects of daptomycin on circulating immune cells were occasionally observed in rats and dogs. Nonetheless, considering its antibiotic activity, it was considered possible that administration of

daptomycin to normal healthy rats and dogs could be associated with slight effects on immune-system related parameters because of a decrease in normal bacterial flora.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

Testing of daptomycin for genotoxicity with a battery of tests in bacteria, mammalian cells, and *in vivo,* did not reveal genotoxic effects of daptomycin in different concentrations and dose levels.

- Carcinogenicity (with toxicokinetics)

No carcinogenicity studies have been conducted with daptomycin in view of the expected short duration of treatment (less than 6 months). This is consistent with the current international guidelines on carcinogenicity testing.

- Reproductive and developmental studies

Daptomycin administered by *iv* bolus injection had no effect on fertility parameters in male and female rats. NOAEL for reproductive effects was 150 mg/kg/day and for parental toxicity < 25 mg/kg/day. Effects on offspring were limited to a transient decrease in body weight at 150 mg/kg/day. This effect which was attributed to maternal toxicity was reversible 14 days postpartum.

Two teratology studies were conducted in rats and rabbits with doses up to 75 mg/kg/day during organogenesis. Daptomycin was not teratogenic in either species. The NOAEL for maternal toxicity was 20 mg/kg/day and for teratogenic effects 75 mg/kg/day.

The effects of daptomycin on peri and post-natal development were evaluated in rats receiving daily intravenous bolus injection of daptomycin with dose level up to 75 mg/kg/day. Reproduction was not affected in the F0 animals, and no treatment-related developmental toxicity was noted in the offspring. No treatment-related effects were observed with respect to fertility of F1 dams. NOAEL for peri- and post-natal effects was 75 mg/kg/day, and for parental toxicity 2 mg/kg/day.

Toxicokinetic analyses were not conducted during the reproductive toxicity studies. However, data from other studies suggest that the doses used in the reproductive toxicity studies resulted in high plasma levels.

Although these data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development, in the absence of clinical data on pregnancies, daptomycin should not be used during pregnancy unless clearly necessary as recommended in the Summary of Product Characteristics.

- Local tolerance

In repeat dose toxicity studies there was no evidence of local injection site irritation. Local administration of daptomycin to rabbits resulted in slight, reversible skin irritation (200 mg/kg daptomycin) and eye irritation (11 particulate daptomycin).

- Other toxicity studies

A dose range-finding study showed that juvenile dogs were not affected by daptomycin at daily doses up to 75 mg/kg for 14 days. In contrast to these findings, the pivotal study revealed lesions in both peripheral nerves and spinal cord in juvenile dogs of the same age that received 50 mg/kg/day for 28 days. The dose level at which skeletal muscle lesions occurred (150 mg/kg/day) exceeded that of nerve lesion occurrence (50 mg/kg/day), and the skeletal muscle degeneration was not accompanied by increase in CPK activity. This indicates that juveniles are more sensitive than adults to daptomycin-induced nerve lesions. Additionally, as already mentioned, the comparative pharmacokinetics data revealed that total systemic clearance appears to be faster in juvenile dogs as compared to adults.

Daptomycin appeared to have limited potential for phototoxicity or immunotoxicity, and exhibited low immunogenicity upon repeated administration

Ecotoxicity/environmental risk assessment

An assessment of the risk was performed and no significant risk to the environment related to the use of daptomycin is anticipated. The potential risk of resistance developing in the environment following renal excretion of daptomycin cannot, however, be ruled out.

4. Clinical aspects

Introduction

The clinical development of daptomycin was initiated in the 1980s but was later terminated by the sponsor. Clinical development later resumed with a quite different dose regimen intended improve efficacy and minimise the risk of daptomycin-associated myopathy. The application for daptomycin 350 mg and 500 mg vials for intravenous infusion was submitted as a stand alone application seeking a single indication for the treatment of complicated skin and soft tissues infections suspected or known to be caused by Gram-positive bacteria known or likely to be susceptible to daptomycin and when parenteral therapy is necessary.

The clinical programme included:

- A series of pharmacokinetic studies, including single and multiple doses, studies in special populations and interaction studies.
- Two phase II studies in patients with Gram-positive bacterial infections and two dose ranging studies in patients with bacteraemia.
- Two main randomised, controlled studies comparing the efficacy and safety of daptomycin with standard treatments in cSSTI, one of these studies was mainly conducted in the USA whereas the other one was mainly conducted in Europe and South Africa.

All clinical studies were claimed to have been performed according to Good Clinical Practice. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical trials mostly comply with the Note for Guidance on evaluation of medicinal products indicated for treatment of bacterial infections (EWP/ 558/95 rev. 1), even though they were conducted prior to the release of the current version of the Guideline.

The approved indication 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).

Pharmacokinetics

The pharmacokinetic profile of daptomycin has been defined in a series of studies submitted, which enrolled more than 350 adult subjects. An overview of these studies is provided in Table 2. In addition results from interaction studies have been provided as well as a population pharmacokinetics analysis performed on the basis of data from patients enrolled in phase II and III studies.
Daptomycin is for intravenous administration only. In all studies daptomycin has been administered as an *iv* infusion during 30 min.

Table 2: Single- and multiple dose studies

	Study start Location	**Study objective**	**No subjects entered**	**Dose**	**Inclusion criteria**
B8B-LC-AVAL	1991 USA	Protein binding	6	3 mg/kg single dose	Healthy volunteers
B8B-LC-AVAA	1986 USA	Safety PK, single dose	6	5, 10, 25, 50, 75 mg single dose	Healthy volunteers
B8B-LC-AVAF	1987 USA	Dose linearity of single doses	6	0.5, 1, 1.5, 2 mg/kg single dose	Healthy volunteers
B8B-LC-AVAK	1987 USA	Dose linearity Single and multiple doses	6	2, 3, 4, 6 mg/kg single dose 3 mg/bid x 5	Healthy volunteers
DAP-00-02	2000 USA	PK, single and multiple doses	24 (12 M/12 F)	4, 6, 8 mg/kg od 7 or 14 days	Healthy volunteers
B8B-LC-AVAB	1986 USA	PK, multiple doses	10	1 mg/kg od 10 days	Healthy volunteers
B8B-LC-AVAI	1987 USA	Safety and PK at steady state	10	2 mg/kg od 14 days	Healthy volunteers
B8B-LC-AVAP	1990 USA	Safety, PK, multiple doses	14	3 mg/kg bid 14 days 4 mg/kg bid 14 days	Healthy volunteers
B8B-LC-AVAC	1986 USA	Distribution and metabolism	5	1 mg/kg, ^{14}C-labelled single dose	Healthy volunteers
DAP-00-04	2000 UK	Distribution Skin blisters	7	4 mg/kg single dose	Healthy volunteers
DAP-GER-01-11	2002 USA	Effects on aged subjects	24	4 mg/kg single dose	Healthy volunteers: aged and young
B8B-MC-AVAD	1987 USA	PK renal disease	45	1 mg/kg 3 mg/kg single dose	Healthy volunteers and patients with renal impairment
DAP-00-01	2000 USA	PK renal effects	29	4 mg/kg, single dose or two doses	Volunteers with varying degrees of renal function
DAP-MDRI-01-03	2001 USA	PK renal disease (ESRD)	7	4 or 6 mg/kg, then 3 mg/kg every 48 hr (15 days)	Volunteers with ESRD
DAP-MDRI-01-09	2001 USA	Renal handling	8	4 mg/kg od 14 days 6 mg/kg od 14 days	Volunteers with renal dysfunction
DAP-REN-02-03	2003 USA	Tolerability and PK in ESRD	25	8 mg/kg, then 6 mg/kg every other day (19 days)	Subjects with ESRD on stable haemodialysis
DAP-HEP-00-09	2001 USA	Hepatic handling	19	6 mg/kg single dose	Volunteers with hepatic dysfunction
DAP-OBSE-01-07	2002 USA	Effect on obese subjects	25	4 mg/kg single dose	Healthy volunteers: non obese, moderately and extreme obese
DAP-SST-9801-B	2002 South Africa	PK, safety and efficacy in cSSTI patients	16	4 mg/kg od up to 14 days	Patients with cSSTI
*DAP-ADT-04-02	2005, USA	PK, safety at higher doses	36	6,8,10 and 12 mg/kg for up to 14 days	Healthy volunteers

***** Summary information only provided on electrophysiologic end points as full study report was not available
The vast majority of the measurements have been obtained using HPLC analysis.

- Absorption

The pharmacokinetic parameters obtained after single and multiple doses are presented in the Tables 3 and 4.

Table 3: Mean (%CV) PK Daptomycin – single doses

Daptomycin Dose (i.v)	**C_{max} mg/l**	**$AUC_{0-\infty}$ mg-hr/ml**	**T_{max} (hr)**	**$T_{1/2}$ (hr)**	**CLs ml/hr/kg**	**V_{ss} l/kg**
4 mg/kg	54.6	425.3	0.5	7.4	9.6	0.093
	(10.0)	(13.7)	(0.5)	(12.3)	(13.5)	(12.1)
6 mg/kg	86.4	705.38	0.5	7.8	8.6	0.088
	(8.2)	(9.43)	(0.5)	(12.3)	(9.3)	(8.4)
8 mg/kg	116.3	1126	0.5	9.6	7.2	0.091
	(8.7)	(14.3)	(0.5)	(11.14)	(15.3)	(13.68)

Table 4: Mean (%CV) PK Daptomycin – multiple doses

Dose Study Day	**C_{max} mg/l**	**AUC_{0-24} mg-hr/l**	**T_{max} (hr)**	**$T_{1/2}$ (hr)**	**Vz l/kg**
4 mg/kg Day1	54.6	425.3*	0.5	7.4	0.1012
	(10.0)	(13.7)	(0.5)	(12.3)	(13.24)
Day 7	57.8	493.5	0.75	8.1	0.096
	(5.13)	(15.3)	(36.5)	(12.0)	(9.2)
6 mg/kg Day 1	86.4	705.38*	0.5	7.8	0.095
	(8.2)	(9.43)	(0.5)	(12.3)	(9.54)
Day 7	98.6	747.4	0.58	8.9	0.104
	(12.2)	(12.2)	(35.0)	(14.9)	(12.6)
8 mg/kg Day 1	116.3	1126*	0.5	9.6	0.099
	(8.7)	(14.3)	(0.5)	(11.1)	(14.12)
Day 7	133.0	1129.9	0.58	9.0	0.092
	(10.1)	(10.4)	(35.0)	(12.9)	(12.5)
Day 14	129.5	1090.0	1.0	8.86	0.095
	(11.2)	(10.0)	(0.0)	(9.34)	(13.47)

*$AUC_{0-\infty;}$ # %CV not available

Daptomycin pharmacokinetics appeared to follow a two-compartment model, with a rapid distribution phase followed by a slower elimination phase.

- Distribution

The apparent volume of distribution (Vd), calculated from both single dose and multiple doses studies was about 0.10 l/kg.

Studies with human plasma showed that daptomycin reversibly bound primarily to albumin (90%) at 4 g/100 ml but binding was not concentration dependent. The potential for any interaction between daptomycin and other medicinal products due to displacement of protein binding will be further looked at post-authorisation and reported in the PSURs. There was a trend toward decreasing serum protein binding among subjects with CL_{cr} <30 ml/min (87.6%), including haemodialysis patients

(85.9%) and continuous ambulatory peritoneal dialysis (CAPD) patients (83.5%). However, binding to albumin is weak, with a dissociation constant of 90.3 μM, while binding to Gram-positive bacteria appears to be very strong or even irreversible. This is demonstrated by the small effect of serum proteins on bactericidal activity since minimum inhibitory concentrations (MICs) of daptomycin typically increased by only two doubling dilutions in the presence of 4% human albumin (approximately 75% effective protein binding). Also, arithmetic mean MICs in 95% solutions of human and mouse sera, in 5% human albumin solution and in broth showed that daptomycin was 2-4 fold more active than would be predicted from calculations of free drug concentrations. Thus, the assumption that only the 10% free drug is active may be an underestimate.

- Elimination

In-vitro studies using human hepatocytes showed that daptomycin is neither an inhibitor nor an inductor of cytochrome P450 isoenzymes. A study with human hepatic microsomes showed no loss of daptomycin in the presence or absence of NADPH, suggesting lack of involvement of CYP450 in the metabolism of daptomycin.

In a study in healthy volunteers given 6 mg/kg daptomycin daily, four peaks that were detected at low concentrations in urine appeared to reflect phase I oxidative metabolites (either hydroxylated or N-oxidated), perhaps some enzymatic hydrolysis and a fragment of daptomycin. Since no systemic metabolism by CYP450 was observed, it has been proposed that catabolism of daptomycin might be occurring during renal excretion or within the urinary bladder.

Daptomycin is primarily eliminated by the kidney. In the radiolabeled daptomycin study, 86% of the dose was recovered, with 78% in urine, 5% in faeces and 3% in breath. Of the 78% excreted in the urine, 52% was biologically active according to the microbiological assay. The rest appeared in the urine as a biologically undetectable ^{14}C entity that is proposed to represent peptide fragments produced after renal excretion. The plasma elimination half-life of daptomycin determined from total radioactivity was 8.8 h compared to 7.6 h as determined from the microbiological assay. The whole blood ^{14}C elimination half-life was about 9.1h.

Although the risk to infants exposed to daptomycin via breast-milk is expected to be limited, the lack of definitive data led to a recommendation that breastfeeding should be discontinued during treatment.

- Dose proportionality and time dependencies

The single and multiple doses data showed approximately linear pharmacokinetics up to 8 mg/kg daptomycin.

Trough concentrations showed that steady state was achieved on day 4, i.e. prior to the fourth dose. No clear time-dependent accumulation (from day 4 and onward) was observed. The mean (± SD) steady state trough concentrations (days 4 to 8) attained following administration of 4, 6, and 8 mg/kg once daily were 5.9 (± 1.6), 9.4 (± 2.5), and 14.9 (± 2.9) mg/l, respectively. The accumulation factor within a given dose from Day 1 to Day 7 was approximately 20%.

The between-subject variability in the pharmacokinetic parameters was generally low in healthy volunteers (% CV < 15 %).

- Special populations

Renal impairment

From the studies that provided pharmacokinetics data in patients with renal impairment, clearance decreased while AUC and half-life increased with decreasing renal function with a linear relationship between clearance and creatinine clearance. Correspondingly, urinary excretion dropped from 50% to 22% in subjects with moderate to severe renal insufficiency. The fraction of the dose cleared by haemodialysis ranged from 11-28% indicating that these patients should not require a dose adjustment

on dialysis days. Probenecid had no effect on the pharmacokinetics of daptomycin, suggesting that tubular secretion was not involved in daptomycin elimination.

A population pharmacokinetics analysis was performed based on data obtained from 282 adult subjects – 153 from nine Phase I studies (conducted by Cubist) and 129 from six Phase II-III studies. The best fit to the data was a two-compartment linear model with first order elimination. The analysis confirmed the relationship between daptomycin clearance and creatinine clearance.

The volume of distribution increased in patients as compared to healthy volunteers such that AUC values in patients with infection and CLcr >40 ml/min were on average 13 to 24% lower compared to matched healthy subjects. An even greater difference in AUCs was observed between patients and volunteers (35-47% lower compared to healthy volunteers) in subgroups with severe renal impairment or with ESRD. However, the difference observed was based on small numbers per group.

Based on the final model from the population PK analysis the predicted plasma concentration-time profiles were plotted against renal function (RF) category (RF1: CrCl ≥ 80 ml/min, RF2: CrCl ≥ 50 to < 80 ml/min, RF3: CrCl ≥ 30 to <50 ml/min, RF4: CrCl <30 ml/min, RF5: end stage renal disease, ESRD). It was concluded that:

- The mean plasma concentration-time profiles in patients with mild and moderate renal impairment (RF2 and RF3 categories) were similar to those for healthy volunteers.
- The median exposure in those with CrCl ≥ 30 to <50 ml/min was approximately 20% higher than seen with normal renal function (501µg.hr/ml vs 410 µg.hr/ml) but this difference was within the between subject variability (CV >30%). This finding contrasts with an increase in AUC by 65% in RF3 subjects compared to RF1 subjects in a clinical study in which the analytical method used was different. Thus there remains uncertainty regarding the true potential for increased exposure to daptomycin in those with CrCl 30-50 ml/min and caution is advised in the Summary of Product Characteristics.
- The profiles for patients with severe renal impairment (RF4) and for ESRD patients (RF5) diverged noticeably from profiles in healthy volunteers (RF1).
- The median C_{max} values for each of the renal function category were comparable following a 4 mg/kg q24h dosing regimen (ranging from 49 to 54 µg/ml).

Steady state simulated exposure (over one dosing interval) for patients with severe renal impairment (RF4) and with ESRD (RF5) is shown in the Table 5.

Table 5: Simulated AUC Estimates by Dosing Regimen and Renal Function Category

Renal Function	4 mg/kg q24hr	4 mg/kg q36hr	4 mg/kg q48hr	3 mg/kg q36hr	3 mg/kg q48hr	2 mg/kg q24hr	4 mg/kg LD + 3 mg/kg q48hr
1	427	N/A	N/A	N/A	N/A	N/A	N/A
4	840	790	780	592	585	420	595
5	978	991	949	743	712	488	734

Overall it was agreed that for patients with creatinine clearance ≥ 30 ml/min no dose adjustment is required but, due to limited clinical experience, response to treatment and renal function should be closely monitored in all patients with some degree of renal insufficiency (creatinine clearance < 80 ml/min). For patients with creatinine clearance < 30 ml/min, including patients on haemodialysis or CAPD the dose should be reduced to 4 mg/kg administered as a single dose once every 48 hours. These dose recommendations are based on modeling data. Nonetheless it was agreed that daptomycin should only be used in such patients if necessary and clinical response to treatment and renal function should be closely monitored in these patients. The applicant also committed to provide further efficacy and safety data in patients with renal insufficiency as part of the follow-up measures to be submitted post-authorisation.

Elderly

While daptomycin C_{max} was similar between age groups, the mean AUC_{0-t}, AUC (0-∞) and plasma half-lives were higher in geriatric subjects (CrCl 31-75 ml/min) compared with younger subjects (CrCl 75-115 ml/min). In parallel, plasma and renal clearance and the fractions of the dose excreted in urine were lower in geriatric subjects. However, the volume of distribution (V_z and V_{ss}) was similar between ages. It appeared that the effect of age on AUC was due to age-associated decreases in renal function. Therefore no dose adjustment is recommended in the elderly per se except those with severe renal impairment. However as further discussed there are limited efficacy and safety data in elderly.

Table 6: Mean (%CV) PK Daptomycin in Young and Elderly Subjects

Dose Group	**C_{max} mg/l**	**$AUC_{0-\infty}$ mg-hr/l**	**T_{max} (hr)**	**$T_{1/2}$ (hr)**	**V_{ss} l/kg**	**CLr ml/hr/kg**	**CL ml/hr/kg**
Geriatric	43.98	473.66	0.53	11.85	0.15	4.27	9.86
	(16.67)	(23.21)	(7.48)	(18.98)	(26.83)	(39.97)	(25.09)
Young	42.32	300.64	0.55	6.79	0.14	7.20	15.09
	(15.35)	(11.53)	(27.64)	(7.78)	(12.86)	(23.53)	(16.93)

Hepatic impairment

Results from an open label, single dose study (6 mg/kg) showed that moderate hepatic impairment (Child-Pugh B) did not affect daptomycin pharmacokinetics. There are no data in subjects with severe hepatic impairment and therefore daptomycin should be used with caution in this population as mentioned in the Summary of Product Characteristics.

Gender

Study DAP-00-02 did not demonstrate any important gender effect on daptomycin pharmacokinetics ($p > 0.16$). The population pharmacokinetic analysis indicated that the average CL was approximately 20% faster in males than females but the mean AUC calculated from the 4 mg/kg data in males (477 ± 280 µg/ml·hr) was only 10% lower compared to females (528 ± 250 µg/ml·hr). Furthermore, the magnitude of this difference was small relative to the variability among subjects (coefficient of variation ≥ 47%). No dosage adjustment based solely on gender is therefore warranted.

Weight

In obese patients, administration of single 4 mg/kg doses to groups with BMI <25, 25 to 40 and > 40 kg/m^2 but with CrCl >70 ml/min showed that the $AUC_{0-\infty}$ daptomycin was increased in obese subjects compared with non-obese matched control subjects and reached statistical significant for extremely obese subjects. In the population PK analysis, there were 29 extremely obese individuals found compared to 333 moderately obese and 255 non-obese. Body weight was identified as a potential factor influencing inter-compartmental clearance and the volume of the peripheral compartment. *Post hoc* estimates suggested that the mean AUC in moderately obese subjects was 28% higher and the mean AUC in extremely obese subjects was 42% higher. However, increases in both groups were within the variability observed (coefficient of variation = 55% in normal subjects). Dose adjustment based on obesity alone was considered unnecessary in moderately obese subjects. Since in very obese, the AUCs observed would not be expected to pose a safety risk whereas there is a risk of failure of therapy if doses are reduced unnecessarily, no dose adjustment is recommended however the limited data available are reflected in a cautionary statement in the Summary of Product Characteristics.

Paediatric population

No studies have been conducted to evaluate the pharmacokinetics of daptomycin in children but the applicant undertook to provide the results from a planned study as part of the follow-up measures to be fulfilled post-authorisation.

- Pharmacokinetic interaction studies

Considering that daptomycin undergoes no CYP450 mediated metabolism and that it does not inhibit or induce CYP450, the potential for pharmacokinetic drug interactions appears to be low.

There was no evidence of interaction between aztreonam (1000 mg, single IV dose) and daptomycin (6 mg/kg, single IV dose) as evaluated in a three-way, crossover study involving 18 healthy subjects.

There was no evidence of interaction between daptomycin (6 mg/kg, multiple IV dosing) and warfarin (25 mg, single PO dose) as evaluated in two-9 day treatment periods involving 16 healthy subjects. No significant pharmacokinetic changes were observed for S- or R-warfarin.

There was no evidence of interaction between daptomycin (4 mg/kg, multiple IV dosing) and simvastatin (40 mg, multiple PO dosing) as evaluated in 20 patients on stable lipid-lowering therapy as a part of a study investigating a potential pharmacodynamic interaction between the two compounds.

There was no evidence of interaction between daptomycin (4 mg/kg, single IV dose) and tobramycin (1 mg/kg, single IV dose) as evaluated in an open label, crossover design study involving six healthy subjects.

There was no evidence of interaction between daptomycin (1 or 2 mg/kg, single IV dose) and amikacin (500 mg, single IV dose) as evaluated in twelve healthy subjects as part of an open label, crossover design an part of a study investigating synergistic bactericide effects.

Because daptomycin is primarily cleared by renal filtration, caution is advised when daptomycin is co-administered with any other medicinal product known to reduce renal filtration as recommended in the Summary of Product Characteristics.

Pharmacodynamics

- Mechanism of action

Daptomycin is an antibiotic with a novel mechanism of action in that it inserts into the cytoplasmic membrane of Gram-positive cells (aerobes and anaerobes), resulting in dissipation of the membrane potential, efflux of potassium ions and bacterial cell death. The antibacterial activity of daptomycin requires the presence of free calcium (as Ca^{2+}) and so sensitivity test media must be supplemented appropriately. Broth supplemented with 50 mg/l calcium has a free (ionised) calcium concentration of 1.10 mM, which is close to the normal range found in human serum (1.15-1.31 mM).

- Primary and Secondary pharmacology

Concentration-dependent bactericidal activity of daptomycin has been documented, including against *S. aureus* (99.9% drop in viable count at 2 x MIC within 30 min) and against vancomycin-resistant enterococci (VRE; within 1 h at 4 x MIC). There is also a concentration-dependent post-antibiotic affect (PAE) of up to 6 h against *E. faecalis* and *S. aureus* at concentrations ranging from 0.25-15 mg/l. In animal models, daptomycin was effective against infections due to Gram-positive bacteria in the blood, skin and soft tissue and kidney at estimated exposure levels equal to or less than that achieved in human with the clinical dose of 4 mg/kg every 24 h.

The in-vitro activity of daptomycin against Gram-positive bacterial pathogens was similar in the US and Europe.

Table 7: Daptomycin Activity Against Selected Pathogens in Europe[a] and the US, from the SECURE Studies

Organism **Resistance phenotype**	**US or EU**	**N=**	**MIC Range (mg/l)**	**MIC_{50}**	**MIC_{90}**
S. aureus					
Oxacillin-Susceptible	US	713	0.03- 0.5	0.25	0.25
	EU	888	≤0.015-1.0	0.25	0.5
Oxacillin-Resistant	US	305	0.12- 0.5	0.25	0.5
	EU	334	0.12- 1.0	0.25	0.5
Coagulase-negative Staphylococci					
Oxacillin-Susceptible	US	356	≤0.015-2.0	0.25	0.5
	EU	486	0.03- 1.0	0.25	0.5
Oxacillin-Resistant	US	770	≤0.015-2.0	0.25	0.5
	EU	554	0.03-1.0	0.25	0.5
E. faecalis					
Vancomycin-Susceptible	US	2,049	0.03-4.0	1.0	2.0
	EU	1,798	≤0.015-4.0	1.0	2.0
Vancomycin-Resistant	US	40	≤0.015-2.0	1.0	2.0
	EU	40	0.5-4.0	1.0	2.0
E. faecium					
Vancomycin-Susceptible	US	147	0.06-8.0	2.0	4.0
	EU	333	0.03-8.0	2.0	4.0
Vancomycin-Resistant	US	219	0.25-4.0	2.0	4.0
	EU	114	0.25-4.0	2.0	4.0
S. pneumoniae					
Penicillin-Susceptible	US	728	≤0.015-0.25	0.12	0.12
	EU	619	≤0.015-1.0	0.12	0.25
Penicillin-Intermediate	US	248	≤0.015-0.5	0.12	0.25
	EU	165	0.03-0.5	0.12	0.25
Penicillin-Resistant	US	187	≤0.015-0.25	0.12	0.12
	EU	81	0.06-1.0	0.12	0.25
S. agalactiae (Lancefield Group B)	US	273	0.03-0.5	0.12	0.25
	EU	367	0.06-1.0	0.25	0.25
S. pyogenes (Lancefield Group A)	US	484	≤0.015-0.5	0.03	0.06
Viridans group streptococci	US	369	≤0.015-2.0	0.25	1.0

a Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and UK.

Resistance

Daptomycin-resistant variants (8 to 32-fold increase in MIC) of *S. aureus* have been generated following a minimum of 20 serial passages or through chemical mutagenesis. Some of these mutants had lost significant virulence. In others, resistance in vitro exceeded the detectable change in in-vivo susceptibility.

In the clinical trials, the development of resistance during treatment occurred twice among > 1000 patients but by mid-2005 there were eight reports of possible resistance in *S. aureus* since launch in the USA in September 2003. Most of these post-treatment isolates were reported as having daptomycin MICs of 4 mg/l.

In addition, results that became available from a study of up to 6 weeks therapy with daptomycin at 6 mg/kg/day in patients with infective endocarditis or bacteraemia revealed eight patients who had *S. aureus* that appeared to acquire increased daptomycin MICs (by 4-16-fold) while on study. Seven of these eight were treated with daptomycin but one received vancomycin. Six out of seven of the daptomycin patients were judged as failures at test of cure (TOC) although the reduced susceptibility

may or may not have contributed to their failure to respond to therapy. The patient treated with vancomycin was judged a success at TOC. Of the six failures on daptomycin, five had MRSA. There is therefore a potential for selection of resistant organisms when daptomycin monotherapy is used for difficult to treat infections and/or for prolonged periods.

Pharmacokinetic/pharmacodynamic

The three initial *in vivo* studies submitted based on the *S. aureus* immunosuppressed mouse thigh infection model concluded that the parameter most predictive of clinical efficacy was the ratio of the 24 h AUC/MIC. However, the AUC/MIC ratio calculated by the three groups differed substantially. Therefore, a new study was performed with five S. aureus with MICs from 1 µg/ml to16 µg/ml. The results indicated that higher AUCs of daptomycin were required to treat *S. aureus* with MICs at 4, 8, and 16 µg/ml but the AUC required for treating infections with *S. aureus* with daptomycin MICs ≤ 2 µg/ml remained constant.
AUCs in patients may be up to 30% lower than the mean in healthy volunteers (after 4 mg/kg the mean daptomycin AUC was 383 µg.h/ml in patients versus 494 µg.h/ml in healthy volunteers) but it was considered that daptomycin levels should still fall within the therapeutic range based on data from the neutropenic model.

Taking all the *in vitro* and PK/PD data into account, the CHMP and EUCAST (European Committee on Antimicrobial Susceptibility Testing) agreed that the breakpoints for susceptibility for staphylococci and for those streptococci relevant to the indication should be susceptible ≤ 1µg/ml and resistant > 1 µg/ml.

Given the insufficient evidence of daptomycin's clinical effect against *Enterococcus faecalis* and *Enterococcus faecium* and the fact that enterococci are considered to be of dubious relevance for the clinical indication no breakpoints have been set.

Due to the pre-clinical observations of effects on nerves, a study in healthy volunteers (120 - 60 daptomycin, 60 controls) assessed peripheral nerve function and cardiac repolarisation during administration of daptomycin at 6 mg/kg daily for 14 days or a normal saline placebo. A blinded review of the data concluded that daptomycin did not induce functional deficits consistent with myopathy or neuropathy or any clinically meaningful change in cardiac repolarisation. For nerve function endpoints, changes from baseline to days 14 and 28 were very small although there was a significantly greater increase in the symptoms and deficit total score in the daptomycin group (0.7 *vs* -0.6 for placebo; p=0.024). QTcB data indicated a slightly greater shift from baseline in the placebo group on day 14 but no subject had an increase > 60 ms on this day.

Clinical efficacy

- Dose response study(ies)

There were no dose-finding studies specific to the indication sought. The rationale for the choice of the dose 4 mg/kg once daily is therefore based on early studies performed in Gram positive bacterial infections including some patients with complicated skin and soft tissues, PK/PD considerations and safety concerns. These early studies conducted showed that 2 mg/kg once daily seemed effective against cSSTI but not in patients with concurrent bacteraemia. While 3 mg/kg twice daily was as effective as standard therapy in patients with bacteraemia, 4 mg/kg once daily was as effective as 3 mg/kg twice daily in such patients. With respect to the safety concerns, the frequency and severity of muscle effects increased with dose fractionation and decreased with once daily dosing in the dog and experience in man indicated that 8 mg/kg once daily for 14 days did not give symptomatic myopathy in six subjects whereas 4 mg/kg twice daily gave this reaction in 2/5 subjects.

- Main study(ies)

The two studies pivotal to the indication sought (cSSTI) were investigator-blinded, randomised, multi-centre studies of very similar but not identical design. An overview of these studies is provided in Table 8.

Table 8: Main studies of Daptomycin in cSSTI

Study Number	**Phase**	**Design**	**Dose of daptomycin**	**Start / End dates**	**Regions where conducted**	**Total subjects (No. received daptomycin)**
DAP-SST-9801	III	Randomised, single-blind, multicentre study vs vancomycin or penicillins	4 mg/kg once daily	Mar 1999 – Aug 2001	USA (64 centers) and South Africa (5 centers)	547 (265)
DAP-SST-9901	III	Randomised, single-blind, multicentre study vs vancomycin or penicillins	4 mg/kg once daily	Mar 2000 – Dec 2000	39 sites in Europe (Austria, Czech Republic, France, Germany, Hungary, Russia, Slovak Republic, Spain and UK), 20 sites in South Africa sites in Australia 3 sites in Israel.	571 (269)

METHODS

Study Participants

The studies enrolled adult patients with a diagnosis of cSSTI known or suspected (based on Gram strain) to be due to Gram-positive bacteria. Entry criteria are summarised in Table 9.

Table 9: Entry criteria

	cSSTI Studies	
Inclusion criteria	**9801**	**9901**
Diagnosis of a Gram-positive bacterial skin and soft tissue infection with some complicating factor e.g. pre-existing skin lesion, an underlying condition that adversely affects delivery of drug to the affected area, the immunological response, or the tissue healing response.	✓	✓
At least 3 of the following signs and symptoms: pain; tenderness to palpation; fever; WBC count >12,000/mm^3 or >10% bands; swelling; erythema (>1cm beyond wound edge); induration; pus formation.	✓	✓
Diagnosis of a cSSTI of sufficient severity to require hospitalisation with parenteral antimicrobial therapy for at least 4 calendar days.		✓
Exclusion criteria		
Burn wound infections that are third degree in nature	✓	✓
Bacteraemia	✓	✓
Furuncle, simple abscess, acne, impetigo, erysipelas, or other minor superficial infection	✓	✓
Cellulitis, not associated with complicating factors	✓	✓

Although bacteraemia was an exclusion criterion, those patients who were found to be bacteraemic post-baseline could continue in the studies.

Randomisation was stratified based on whether the primary diagnosis was infected diabetic ulcer or not.

Patients were not prospectively classified according to overall severity at baseline and enrolment was not stratified. The criteria used to define severe infections were slightly different in both studies. In study 9801 one or more of the following conditions were required:

1. positive blood cultures at baseline
2. fulfilment of the published definition for systemic inflammatory response syndrome (SIRS) by having 2 or more of the following findings: temperature >38°C or <36°C; heart rate >90 beats/minute; respiration rate >20 breaths/minute; or white blood cells (WBC) ≥12 x 103/µl or <4 x 103/µl or >10% bands)
3. at least 3 of 8 physical signs at the primary site of infection assessed as "severe"

In Study 9901, the first two conditions applied and for the third, patients had to have severe tenderness, erythema or swelling.

Treatments

Eligible patients were randomised 1:1 to receive either daptomycin 4 mg/kg daily by *iv* infusion over 30 min or the comparator. Prior to randomisation the blinded investigator was expected to choose the appropriate comparator selected from a list based on local availability and normal treatment practice, dose, and regimen to be used if the patient was randomised to comparator. Options were:

- Vancomycin 1g i.v. q12h
- Oxacillin 4-12g per day i.v. in equally divided doses
- Cloxacillin 4-12g per day i.v. in equally divided doses
- Nafcillin 4-12g per day i.v. in equally divided doses (9801 only)
- Flucloxacillin 4-12g per day i.v. in equally divided doses (9901 only).

Patients with creatinine clearance of 30 to 70 ml/min were to receive a modified dosing regimen for daptomycin (4 mg/kg loading dose, followed by 3 mg/kg q36 hr). Vancomycin dosing was to be adjusted according to a published monogram or results of therapeutic drug monitoring. Subjects with CLCR <30 ml/min were excluded from the study.

In both studies, patients with polymicrobial infections proven or suspected to involve Gram-negative and/or anaerobic bacteria as well as Gram-positive organisms could receive concomitantly aztreonam or metronidazole or both as necessary.

Both protocols provided for a switch to oral medication if certain criteria were met.

The duration of intravenous therapy was to be 7 to 14 days for both regimens (daptomycin or comparator), with the actual duration based on investigator judgment of the subject's response. If, in the investigator's opinion, a subject required more than 14 days of therapy, the duration of therapy could be extended following discussion with the medical monitor.

Objectives

The primary objective for both studies was to demonstrate non-inferiority of daptomycin to that of vancomycin or selected semisynthetic penicillins in the treatment of cSSTI due to Gram-positive bacteria. Daptomycin was to be considered non-inferior to the comparator agents if the lower margin of the 95% confidence interval for the difference in success rates between treatment groups was above 10% for the primary endpoint.

Outcomes/endpoints

A blinded investigator at each site performed all evaluations of clinical signs and symptoms, determined the duration of therapy, assessed clinical outcomes and established the relationship of adverse events to study therapy. The End-of-therapy (EOT) visit was done within 3 days of the last dose of study drug. The Post-Therapy (test of cure, TOC) visit was conducted 7 to 12 days post-treatment. The Post-Study visit was conducted 21 to 28 days post-treatment and was performed only for those cured or improved at TOC.

The following definitions were used for clinical responses at EOT and TOC visits:

Cure: Resolution of clinically significant signs and symptoms associated with the skin infection at baseline (return to pre-infection baseline).
Improved: Partial resolution of clinical signs and symptoms of the skin infection so that no further antibacterial therapy was required.
Failure: Inadequate response to therapy.
Unable to Evaluate: Unable to determine because lost to follow-up.
Failures were "carried forward" regardless of subsequent assessments.

Before unblinding the studies, the Sponsor reviewed the clinical data with respect to validity of diagnosis, diagnostic group, valid pathogens, confounding concomitant medications or procedures, population assignment and outcomes.

Populations for analysis were:

Intent-to-Treat Population (ITT): all treated patients who had a cSSTI. Modified Intent-to-Treat Population (MITT): all ITT patients with a Gram-positive pathogen isolated at baseline.
Clinically Evaluable Population (CE): all ITT patients for whom the clinical outcome could be inferred to reflect the effect of the study compound.

Patients were considered clinically evaluable clinical successes if they had not received potentially effective non-study antibiotics for any other reason had received ≥4 days of study medication (with at least 80% dose compliance in Study 9901) and were judged to be cured or improved by the investigator at TOC.

Patients were considered evaluable clinical failures if they met one or more of the following criteria: outcome judged a failure by the investigator at any time up to and including the TOC visit or received potentially effective non-study antibiotics for lack of efficacy and/or had the primary site of infection surgically removed, and/or had no evaluation after the EOT.

Microbiologically Evaluable Population (ME)
All CE patients with a Gram-positive pathogen at baseline.
The primary endpoint was the Sponsor- defined clinical outcome at the test- of- cure evaluation.

Sample size

The sample size of each study was calculated to provide sufficient patients to conclude that daptomycin was at least as effective as the comparator based on clinical success rates.

RESULTS STUDY 9801

Participant flow

A total of 547 subjects were randomised to study treatment. Disposition of patients is presented in Table 10

Table 10: Summary of Subject Populations (Study 9801)

Disposition	**Daptomycin**		**Comparator**	
Randomised	272		275	
Randomised Not Treated	8		9	
Intent-to-Treat (ITT)	256		261	
Modified Intent-to-Treat[a] (MITT)	209	81.6%	212	81.2%
Clinically Evaluable (CE)	223	87.1%	222	85.1%
Not Clinically Evaluable	33	12.9%	39	14.9%
Microbiologically Evaluable (ME)	187	73%	189	72.4%
Not Microbiologically Evaluable	69	27%	72	27.6%

a. Percentages calculated using ITT population

The two treatment groups were well balanced with regard to age, weight, gender, and race. There were no apparent differences between the treatment groups in the proportion of subjects who discontinued therapy or in the reasons for discontinuation (mainly due to adverse events or clinical failure).

Eight signs (tenderness, erythema, oedema, purulent drainage, fluctuance, induration, ulceration, and necrotic tissue) and 6 symptoms (localised pain, swelling, drainage, redness, chills, and fever) of infection were assessed at each evaluation. The two treatment groups were statistically comparable for all these baseline factors, except purulent drainage which was present in 76% of the subjects in the daptomycin group compared to 84% of the subjects in the comparator group and fluctuance (in 47% and 40% in respective groups) but there were no difference in proportions with moderate or severe scores for these signs. Just over one third of patients per group (35% and 38%) had fever at baseline. There was a slight numerical inferiority for the daptomycin group with respect to proportions with diabetes or peripheral vascular disease at baseline.

Primary diagnoses of cSSTI

The Sponsor-determined diagnoses placed wound infections as commonest (42% in daptomycin versus 50% in comparator), followed by major abscesses (24% *vs* 17%), infected diabetic ulcers (13% *vs* 15%), other ulcers (14% *vs* 13%) and other infections (8% *vs* 5%). There were 50% on daptomycin and 53% on comparator that met the criteria for severity. Over 40% per group were classified as having systemic inflammatory response syndrome (SIRS).

Microbiology

Gram-positive organisms were cultured from 431/530 patients (81%). The most frequently isolated pathogen was *S. aureus* (73% daptomycin group *vs* 69% comparator group) and MRSA accounted for around 16% of all pathogens.

Treatment compliance

Of 256 ITT patients that received daptomycin, 215 (84%) received 4 mg/kg daily throughout the study and 41 (16%) had the regimen adjusted due to renal insufficiency. Of the 260 that received comparative therapy, 40% received semi-synthetic penicillins (mainly oxacillin or nafcillin) while 60% received vancomycin (a small number appear to have received both vancomycin and a penicillin at some time during the period of therapy). Treatment was administered for 7-14 days in 65% on daptomycin and on comparators while 15% and 17% per group were treated for > 14 days. There were only 22 (9%) and 32 (12%) per group who switched to oral therapy, mainly to allow hospital discharge. Similar proportions (32% per group) received aztreonam and/or metronidazole and 40% in each group had adjunctive surgical treatment.

Outcomes

Sponsor-assigned clinical outcomes in the CE and MITT populations at TOC gave 95% confidence intervals within 10% while cure rates were numerically similar between treatments (Tables 11 and 12). In both populations, cure rates were slightly higher in the daptomycin group. In the ITT population, success rates were 65% and 64% with 95% CI at -9.9, 6.6.

Table 11: Clinical response at Test-of Cure in MITT population (Study 9801)

Analysis	**Daptomycin N = 209**	**Comparator N =212**	**95% CI**
Clinical success	140 (67%)	142 (67%)	(-9.0, 9.0)
Cure	91 (44%)	85 (40%)	
Clinical improvement	49 (23%)	57 (27%)	
Clinical failure*	69 (33%)	70 (33%)	

*documented failure in 22% per group

Table 12: Clinical response at Test-of Cure in CE population (Study 9801)

Analysis	**Daptomycin N = 223**	**Comparator N =222**	**95% CI**
Clinical success	167 (75%)	166 (75%)	(-8.2, 8.0)
Cure	110 (49%)	100 (45%)	
Clinical improvement	57 (26%)	66 (30%)	
Clinical failure	56 (25%)	56 (25%)	

At TOC, in the MITT population, investigator-assigned success rates were 72% per group with 95% CI at -8.6 and 8.5 while cure rates were 46% for daptomycin and 43% for comparative therapy. At the post-study visit the investigators considered that 95% and 93% per group had a sustained cure.

Clinical success rates by treatment group were also compared for subjects who did or did not receive oral treatment following i.v. therapy. Success rates were 67% per group for MITT patients not switched to oral therapy with rates of 12/18 (67%) for daptomycin and 17/24 (70%) for those in the comparative group who switched. For those with a successful outcome and no switch to oral therapy, the median durations of treatment were 9 days for daptomycin (n=128) and 10 days for comparators (n=125).

Analyses of sponsor- defined clinical outcomes were also performed for subject subgroups. Severe infections and patients with SIRS responded less well and the differences compared to those with non-severe infections or no SIRS were greater in the comparative group. However, success rates were actually fairly comparable between treatments within these sub-groups. The success rates were lower in patients over 65 years treated with daptomycin (see Table 13) The effect of surgical intervention was inconsistent between treatment groups.

Table 13: Clinical success rates at TOC by age and other factors in MITT population (Study 9801)

Analysis	**Daptomycin N = 209**	**Comparator N =212**	**95% CI**
Age <65 Age >65	102/137 (75%) 38/72 (53%)	96/150 (64%) 46/62 (74%)	(-21.1, 0.1) (5.6, 37.3)
Severe Not severe	70/107 (65%) 70/102 (69%)	68/111 (61%) 74/101 (73%)	(-16.9, 8.6) (-7.8, 17.1)
SIRS No SIRS	58/89 (65%) 82/120 (68%)	60/97 (62%) 82/115 (71%)	(-17.1, 10.5 (-8.8, 14.7)
Surgical intervention No Surgical intervention	25/44 (57%) 115/165 (70%)	34/47 (72%) 108/165 (66%)	(-3.9, 35.0) (-14.3, 5.8)
Bacteraemia	1/4 (25%)	4/6 (67%)	

[1]95% confidence interval around the difference in success rate (Comparator - Daptomycin) using normal approximation to the binomial distribution.

There were no significant differences between the treatment groups for subgroups defined by gender.

The Table 14 shows that clinical success rates were lower in both treatment groups but similar between treatments for infections due to MRSA. In the comparative group, 29 of the 35 with MRSA at baseline had been started on vancomycin and 4 had started on a penicillin before being switched to vancomycin.

Table 14: Clinical success rates by infecting pathogen – MITT in 9801

Analysis	**Daptomycin N = 209**	**Comparator N = 212**	**95% CI**
S. aureus	100/150 (67%)	96/147 (65%)	-12.1, 9.4
S. aureus (MSSA)	73/103 (71%)	66/97 (68%)	-15.6, 9.9
S. aureus (MRSA)	17/34 (50%)	18/35 (51%)	-22.2, 25
S. pyogenes	27/33 (82%)	25/35 (71%)	
S. agalactiae	13/17 (77%)	14/21 (67%)	
E. faecalis	13/25 (52%)	19/33 (58%)	

Microbiological response rates by patient in the ME population at TOC were mainly based on presumptive eradications following successful clinical outcomes and so were also very similar between groups.

RESULTS STUDY 99-01

Participant flow

A total of 571 subjects were randomised to study treatment, and 531 completed therapy. The disposition of patients is presented in Table 15. There were no apparent differences between the treatment groups in the proportion of subjects who discontinued drug therapy or in the reasons for discontinuation (mainly due to adverse events or clinical failure)

Table 15: Summary of Subject Populations (9901)

Disposition	**Daptomycin**		**Comparator**	
Randomised	277		294	
Randomised Not Treated	7		2	
Intent-to-Treat (ITT)	270		292	
Modified Intent-to-Treat[a] (MITT)	213	(78.9%)	255	(87.3%)
Clinically Evaluable (CE)	245	(90.7%)	262	(89.7%)
Not Clinically Evaluable	25	(9%)	30	(10%)
Microbiologically Evaluable (ME)	196	(72.6%)	231	(79.1%)
Not Microbiologically Evaluable	74	(27.4%)	61	(20.9%)

a. Percentages calculated using ITT population

The treatment groups were reasonably well matched with regard to subject demographics and baseline signs and symptoms, including severity scores, except that fever was more common in the comparative group at 57% compared to 45% in the daptomycin group. Also, diabetes and peripheral vascular disease were slightly more common in the comparative group.

Primary diagnoses of cSSTI

The Sponsor-designated diagnoses placed wound infections as the most common (42% per group) followed by major abscesses (29% and 27%), non-diabetic ulcers (13% and 14%), diabetic ulcers (9% and 11%) and other infections (7% per group). There were 181 subjects (67%) on daptomycin and 177 subjects (61%) on comparator that met clinical or laboratory criteria for a severe infection.

Microbiology

The most frequently isolated pathogen was *S. aureus* (70% and 68% per group) but MRSA isolation rates were only 2.3% and 4.3%.

Treatment compliance

The mean duration of therapy was shorter in the daptomycin group (7.4 days compared to 8.1 days) among patients with a successful sponsor-assigned outcome at TOC. In the comparative group, overall 78% received semi-synthetic penicillins and 22% received vancomycin. In fact, 149 received cloxacillin, 59 oxacillin, 19 flucloxacillin and 2 received flucloxacillin and vancomycin. There were 46 (17%) patients in the daptomycin group and 64 (22%) in the comparator group that received aztreonam or metronidazole while 20% in each group had adjunctive surgical treatment.

Switch to oral medication was significantly more frequent among subjects in the comparator group (37/292; 12.7%) than in the daptomycin group (20/270; 7.4%); the primary reasons were clinical improvement and subject request.

Outcomes

In the MITT and CE populations, the Sponsor-defined success rates were very similar, with 95% CI within 10%. Cure rates were also very similar but there was a numerical inferiority for daptomycin (Tables 16 and 17). In the ITT population, success rates were 81% in each group (95% CI -6.1, 6.9) while cure rates were 38% and 42% per group.

Table 16: Clinical response at Test-of Cure in MITT population (Study 9901)

Analysis	**Daptomycin N = 213**	**Comparator N = 255**	**95% CI[a]**
Clinical success	180 (84.5%)	214 (83.9%)	(-7.2, 6.0)
Cure	82 (38.5%)	110 (43.1%)	
Clinical improvement	98 (46%)	104 (40.8%)	
Clinical failure	33 (15.5%)	41 (16.1%)	

a.95% confidence interval around the difference in success rates (comparator – daptomycin), without continuity correction, using normal approximation to the binomial distribution. N.B. Negative values denote that daptomycin performed better than comparator.

Table 17: Clinical response at Test-of Cure in CE population (Study 9901)

Analysis	**Daptomycin N = 238**	**Comparator N = 250**	**95% CI[a]**
Clinical success	217 (88.6%)	235 (89.7%)	(-4.3, 6.5)
Cure	103 (42%)	122 (46.6%)	
Clinical improvement	114 (46.5%)	113 (43.1%)	
Clinical failure	28 (11.4%)	27 (10.3%)	

a.95% confidence interval around the difference in success rates (comparator – daptomycin), without continuity correction, using normal approximation to the binomial distribution. N.B. Negative values denote that daptomycin performed better than comparator.

In comparison, the investigator-assigned outcomes at TOC for the MITT population gave clinical success rates of 88.7% and 87.5% (95% CI -7.2, 4.6), with cure rates of 40.4% and 44.7%. At the post-study visit, 5% of clinically evaluable patients (9 and 11 per treatment group) were considered to have relapsed by the investigators. Seven relapsed patients in each group were culture positive, with *S. aureus* isolated from 5 patients in the daptomycin and from 4 in the comparative group.

Among those who received only intravenous therapy, sponsor-assigned clinical success rates were 86% in both treatment groups (95% CI -6.1, 7.2) while rates for those who switched were 9/13 (69%) for daptomycin and 23/33 (70%) in the comparative group.

Analyses based on sponsor- defined clinical outcomes were also performed for subject subgroups (Table 18). Gender did not affect outcomes in this study. Severity and the presence of SIRS did not

seem to markedly influence success rates although those without SIRS did a little better. As in the previous study, the success rates were lower in patients >65 years age group treated with daptomycin. The infections that required surgical intervention responded far less well then those that did not need such action but this effect was seen to a similar extent regardless of the assigned therapy.

Table 18 Clinical success rates at TOC by age and other factors in MITT population (Study 9901)

Analysis	**Daptomycin N = 213**	**Comparator N =255**	**95 % CI**
Age <65	147/169 (87%)	174/206 (85%)	(-9.6, 4.6)
Age >65	33/44 (75%)	40/49 (82%)	(-10.1, 23.4)
Severe	119/141 (84%)	128/153 (84%)	(-9.1, 7.6)
Not severe	61/72 (85%)	86/102 (84%)	(-11.3, 10.5)
SIRS	57/71 (80%)	66/82 (81%)	(-12.4, 12.8)
No SIRS	123/142 (87%)	148/173 (86%)	(-8.7, 6.6)
Surgical intervention	35/46 (76%)	35/51 (69%)	(-25.2, 10.3)
No Surgical intervention	145/167 (87%)	179/204 (88%)	(-5.9, 7.7)
Bacteraemia	3/6 (50%)	3/6 (50%)	

Sponsor-assigned microbiological responses (eradication rates) by patient in the MITT population at TOC were 73% and 75% while in the ME population rates were 80% and 82%. The 95% confidence intervals were within or very nearly within 10% for both comparisons.

The clinical and microbiological outcomes by pathogen are shown below (Table 19). Among the very few MRSA, response rates were 4/5 for daptomycin and 9/11 for comparators.

Table 19: Clinical responses at TOC by pathogen - MITT in 9901

Pathogen **Number of subjects with positive cultures**[a]	**Daptomycin N = 213**	**Comparator N = 255**	**95% CI**
Staphylococcus aureus (all)	123/149 (82.6%)	145/173 (83.8%)	-6.9, 9.5
Streptococcus pyogenes	54/59 (91.5%)	57/68 (83.8%)	-19, 3.6
Streptococcus agalactiae	11/13 (85%)	9/18 (50%)	
Other streptococci	14/20 (70%)	24/28 (86%)	
Enterococcus faecalis	14/20 (70%)	23/28 (82%)	

In the MITT population, 25 and 24 per group were clinical successes at TOC but had persistence of the pathogen. Of these, 38 patients were infected with *S. aureus*, including 21 in the daptomycin group and 17 in the comparative group. The mean study days to the TOC evaluation was 16 days for daptomycin patients compared to 20 days for those in the comparative group but the ultimate time to clearance was similar between the two groups. On this basis, the applicant states that the difference in microbiological clearance rates at TOC was a function of the timing of the visit.

- Analysis performed across trials (pooled analyses and meta-analysis)

Although there were differences between studies 9801 and 9901 including patient characteristics, choice of vancomycin or semi-synthetic penicillins and sponsor's and physicians assessments of outcome some pooling analysis have been done to further address some findings. These are presented in the section related to discussion on the efficacy.

- Clinical studies in special populations

There are currently no data available on the efficacy of CUBICIN in children. The applicant committed to submit future plans for studies in children.

Rates of clinical success and cure were similar for Blacks and Caucasians in 9901. In 9801, success and cure rates were much higher in Blacks and favoured daptomycin. However, multiple regression analysis did not detect an interaction between treatment and race although there was a significant

effect on outcome of co-morbidities, MRSA and geographic area. The factors that might have contributed to the difference in responses to daptomycin in 9801 included a lower incidence of diabetes in Blacks in the daptomycin group (26% *vs* 38%) and more patients in the comparator group had SIRS (52% *vs* 34%).

- Supportive study(ies)

Few supportive studies were submitted but due to limited number of patients involved, they provided limited support for the studies on the efficacy of daptomycin in the treatment of cSSTI due to Gram-positive bacteria.

Discussion on the clinical efficacy

Overall the primary analysis of both studies 9801 and 9901 suggested that daptomycin was as efficacious as the comparator in the treatment of cSSTI however the demonstration of non-inferiority was discussed in the Committee and the following points were raised.

- The pre-defined choice of the MITT population for the primary analysis was questioned. However, results were also shown for the CE population and were satisfactory.

- The use of "improved" as a judgement of outcome and the derivation of clinical success rates, on which the primary comparison of outcomes was based, could be opened for criticism. However, an outcome of improved required that no further antibacterial therapy was necessary. Therefore, the derivation of success rates was deemed acceptable, especially since cure rates were also presented separately in the tabulations.

- Range of diagnoses allowed and the requirement for only 3 of a list of signs and symptoms to be present which might leave open the possibility of enrolling patients with uncomplicated or borderline complicated infections. There is currently a lack of consensus on the definition of what constitutes a complicated SSTI. The inclusion criteria in 9801 and 9901 required the existence of potentially complicating factors. Overall, it was considered that patients enrolled in 9801 and 9901 had cSSTI. In study 9801, 88% in the daptomycin group and 89% in the comparative group had at least 5 signs and symptoms at baseline while 69% and 73% in respective groups had 6 or more. In study 9901, 97% in both treatment groups had at least 5 signs and symptoms at baseline while 90% and 91% per group had at least 6.

- Severity of the infection. While the two protocols varied slightly in the definition of severe infections, applying the same set of criteria for severe infections to both study populations gave similar proportions between studies. Also, there were no major differences between outcomes in patients with severe and non-severe infections who were treated with daptomycin as presented in the results of each study.

- Differences in success rates between 9801 and 9901 that reflected differences in percentages assigned to the improved categories and not to any notable differences in percentages deemed to be cured. The anomaly seemed likely to be related to the fact that the population in 9801 was older, more obese, had more patients with diabetes and peripheral vascular disease, had a higher incidence of SIRS and included more patients with MRSA compared to 9901. These features seem to reflect the fact that 90% of patients enrolled into 9801 came from the US and 10% from S. Africa whereas no US sites were involved in 9901 and 50% of the total enrolled came from S. Africa. The S. African patients were mostly younger and leaner and more often presented with acute trauma.

  In a multivariate analysis there was no effect of randomised treatment on the clinical cure rate and no treatment interactions were present with any of the other potentially prognostic factors included in the model. The most important factors for determination of an outcome of cure were diagnosis of an ulcer (50% decrease in the odds of cure, $p<0.01$) and the presence of peripheral vascular disease (47% decrease in odds of cure, $p<0.01$). There was no treatment effect or treatment by

geographic area interaction detected. Therefore, differences in outcomes between geographic areas were due to other factors, some of which are mentioned above.
Overall, sensitivity analyses adjusting for prognostic factors did not greatly affect the estimated cure rates for each treatment group and therefore the conclusions drawn from the primary analyses are considered robust to the imbalances in some factors seen at baseline.

- In both studies, success rates with daptomycin in patients >65 years appeared lower compared to the < 65 years age group. An analysis of the sponsor-defined clinical outcome in the pooled MITT population showed a lower success rate in the daptomycin group compared to comparator and that responses were particularly poor when the daptomycin dose was reduced.
  The issue of age and efficacy was also examined in the multivariate analysis, which demonstrated that neither age itself nor the age-by-treatment interaction was statistically significant. Thus, the observed difference in efficacy between treatment groups in subjects aged 65 and above would appear not to be due to age *per se* but was the result of several factors that were confounded with age, including the protocol advice to administer reduced doses of daptomycin in those with CL_{CR} >30 ml/min. Overall the CHMP considered that there was no need for dose adjustment in the elderly except in case of renal insufficiency (CrCl < 30 ml/min). Nonetheless because of the limited data on the safety and efficacy of daptomycin in patients aged > 65 years caution is recommended. In addition the applicant has committed to perform an observational study in the elderly with cSSTIs, the results of which will be provided post-authorisation.

- Differences between studies 9801 and 9901 regarding the investigators' pre-assignment of patients to vancomycin (51% in 9801 but 22% in 9901) or semi-synthetic penicillins. Given the low rate of MRSA isolated, concern was raised over the possibility that vancomycin was not optimal therapy for organisms susceptible to many beta-lactam agents. Indeed, clinical and microbiological outcomes according to type of comparative therapy given showed a considerable disadvantage for those given vancomycin and a numerical disadvantage for daptomycin compared to semi-synthetic penicillins, which were chosen for the great majority of comparative group patients in 9901.

Table 20 : Clinical Success (MITT Population)

	Daptomycin	**Vancomycin**	**Semi-Synthetic Penicillins**
Pooled	320/422 (76%)	126/187 (67%)	230/280 (82%)
9801	140/209 (67%)	79/125 (63%)	63/87 (72%)
9901	180/213 (85%)	47/62 (76%)	167/193 (87%)

However, when looked at by pre-randomisation assignment there were lesser differences between treatment groups within the pre-assigned subsets. Also, both studies showed lower success rates in daptomycin and vancomycin groups for those pre-assigned to vancomycin compared to patients pre-assigned to semi-synthetic penicillins.

Table 21: Clinical Success by Pre-Randomisation Assignment (MITT Population)

	All		**Pre-Assignment: Vancomycin**		**Pre-Assignment: Semi-Synthetic Penicillins**	
	Daptomycin	**Comparator**	**Daptomycin**	**Vancomycin**	**Daptomycin**	**Semi-Synthetic Penicillins**
Pooled	320/422 (76%)	356/467 (76%)	77/112 (69%)	126/187 (67%)	226/268 (84%)	230/280 (82%)
9801[a]	140/209 (67%)	142/212 (67%)	43/70 (61%)	79/125 (63%)	80/97 (82%)	63/87 (72%)
9901	180/213 (85%)	214/255 (84%)	34/42 (81%)	47/63 (76%)	146/171 (85%)	167/193 (87%)

a. 42 patients in the MITT population in study DAP-SST-9801 who were randomised to daptomycin had no pre-randomisation assignment data.

The protocol dose of semi-synthetic penicillins was 4-12 g per day. However, 19% of CE patients in 9901 and 8% in 9801 were treated with 2-<4 g/day, probably because the advice to investigators to dose according to local standard of care was sometimes interpreted as treating with the locally approved dose regimen (i.e. 2 g in some countries). Very few (seven patients) received less than 2 g daily. However, a comparison of outcomes restricted to the CE population pre-randomised to semi-synthetic penicillins and to comparative group patients indicated similar efficacy for daptomycin and the chosen beta-lactam agents as shown in Table 22 below.

Table 22

Study 9801	**Daptomycin N=103**	**Comparator N=82**	**95% C.I.**
Success	86 (83%)	68 (83%)	(-11.9, 10.1)
Cure	62 (60%)	41 (50%)	(-24.2, 4.1)
Failure	17 (17%)	14 (17%)	
Study 9901	**Daptomycin N=197**	**Comparator N=170**	**95% C.I.**
Success	174 (88%)	154 (91%)	(-4.2, 8.6)
Cure	84 (43%)	80 (47%)	(-5.7, 14.5)
Failure	23 (12%)	16 (9%)	

- Concomitant use of aztreonam/metronidazole. A multivariate analysis concluded there was no statistical evidence that concomitant aztreonam/metronidazole affected outcome *per se*. However, success rates were lower for the subsets of patients in each of the daptomycin and comparative therapy groups that received aztreonam and/or metronidazole. The pooled data for studies 9801 and 9901 showed that the clinical success rates in patients who did receive aztreonam/metronidazole were 64 % in daptomycin arm compared to 69 % in the comparator (MITT population). Among patients who did not receive these additional agents the rates were 80 % in daptomycin arm compared to 79 % in the comparator. The difference in outcomes appears to reflect the fact that patients who received concomitant aztreonam/metronidazole were more likely to be aged ≥ 75 years, obese, diabetic and/or immunocompromised and were more likely to have peripheral vascular disease or MRSA. More patients in 9801 (32% per group) received aztreonam or metronidazole than in 9901 (17% daptomycin and 22% on comparators). This seems to be consistent with the difference between the US patient population that predominated in 9801 compared to the wholly non-US population enrolled into 9901.

- Enterococci: The role of enterococci in cSSTI might be viewed as dubious but isolation of these organisms from a cSSTI site might be indicative of more complex and chronic infections compared to other types of infections treated. Patients with enterococci had a poorer clinical outcome, especially if treated with daptomycin. However, in addition to the imbalance in diabetes (51% *vs* 42%) and diabetic ulcers (40% *vs* 18%) in the daptomycin group, more patients in this group failed for reasons that were not related to efficacy of the study medication (e.g. under-dosing, died or discontinued before completing therapy) than in the comparator group. The multivariate analysis indicated that although the presence of enterococci was associated with lower clinical success rates there was no difference between daptomycin and comparator. It appears that patients from whom enterococci were cultured had more complex or particular types of infections that could have influenced outcomes. In addition, they might reflect heavily contaminated wounds in which gram-negative organisms were also present.

Clinical safety

- Patient exposure

At the data cut-off date of 1 July 2004, 1474 subjects had received daptomycin in the 23 studies, 1150 received comparator agents and 72 received placebo.

Table 23: Number of subjects in Cubist-sponsored studies by population in Safety Database

	Daptomycin	**Placebo**	**Active Comparator**
Clin Pharm - 13 Studies	253	72	49
cSSTI – 3 studies	550	0	558
CAP – 2 studies	455	0	460
Other - 5 studies	216	0	83
Total	1474	72	1150

There were 121 subjects who received a single dose of daptomycin in the clinical pharmacology studies and 32 patients received less than 24 hours treatment in the clinical studies. However, most (60%) received 7 to 14 days daptomycin and 22% received 2 to 6 days. The total doses ranged from <1 – 4 grams but the majority (81%) received 4 mg/kg once daily. There were 253/1474 (17%) subjects and patients who did not complete planned therapy with daptomycin, with 5% discontinuing due to each of adverse events (AEs) or clinical failure.

In the cSSTI studies, 550/1108 patients received daptomycin and 558 received one or more of the comparators. Over 85% completed intravenous treatment as planned while 12% and 10% per group discontinued early with a similar pattern of reasons (3% of discontinuation were due to AEs in both groups).

- Adverse events

AEs were reported for 790/1474 (54%) that received daptomycin and 620/1222 (51%) treated with comparators or with placebo. Incidences were lowest in the healthy volunteer studies (72/253 [28%] subjects on daptomycin and 40/121 [33%] in comparative groups) and highest in the small studies in patients with various infections and complicated medical histories.
In the two pivotal cSSTI studies, there were 841 AEs in 280/550 (51%) patients treated with daptomycin and 891 AEs in 293/558 (53%) in the comparator groups.

The commonest AEs affected the gastrointestinal tract followed by AEs mapped to general disorders and administrative site conditions and infections and infestations.

In the cSSTI studies there were slightly higher rates of creatine phosphokinase (CPK) and LFT abnormalities with daptomycin. The higher rate of UTI likely reflects the lack of anti-Gram-negative activity of daptomycin.

Table 24: AEs in cSSTI studies 9801 and 9901

Adverse Event	Daptomycin (N=534)	Comparator (N=558)
Gastrointestinal disorders		
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhoea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders		
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous system disorders		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/subcutaneous disorders		
Rash	4.3%	3.8%
Pruritus	2.8%	3.8%
Diagnostic Investigations		
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections		
Fungal infections	2.6%	3.2%
Urinary tract infections	2.4%	0.5%
Vascular disorders		
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/urinary disorders		
Renal failure	2.2%	2.7%
Blood/lymphatic disorders		
Anaemia	2.1%	2.3%
Respiratory disorders		
Dyspnoea	2.1%	1.6%
Musculoskeletal disorders		
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

Among the 790 that received daptomycin and reported an AE, 41% had mild AEs and 34% had AEs of moderate severity while 24% had at least one severe AE. These figures compare with 44%, 40% and 16%, respectively, in the comparative group.

Analysis of data according to durations < 7 days, 7-14 days or > 14 days for the cSSTI studies showed that most types of AEs reported did not increase in frequency in either treatment group when treatment was 7-14 days compared to <7 days. Some types of AEs did increase when either treatment was prolonged to 14 days but the increases seen were not consistently greater in the daptomycin or comparative therapy groups.

Overall, 290/1474 (20.0%) in the daptomycin group and 229/1222 (19%) in the comparative group had an AE possibly or probably related to treatment. Among the populations that reported AEs, drug-related event rates were 37% and 38%, respectively.

The commonest type of AEs considered related affected the gastrointestinal tract (7% of patients per treatment group). Pseudomembraneous colitis has been recorded but data do not indicate a particular risk conferred by daptomycin alone**.** Nausea or diarrhoea (each 2% per group) and vomiting or constipation (each 1% per group) predominated. There was no excess of infusion site problems with daptomycin on comparison with pooled data from all other agents administered.

Table 25: Summary of commonest AEs possibly/probably related to treatment by SOC

	Number (%) of Subjects			
	Total Studies		cSSTI	
	Daptomycin	Comparator	Daptomycin	Comparator
System Organ Class	(n = 1474)	(n = 1222)	(n = 550)	(n = 558)
	n (%)	n (%)	n (%)	n (%)
Any adverse event	290 (20)	234 (19)	99 (18%)	118 (21%)
Gastrointestinal disorders	98 (7)	82 (7)	37 (7%)	41 (7%)
General disorders & administration site conditions	49 (3)	43 (4)	22 (4%)	28 (5%)
Infections & infestations	25 (2)	27 (2)	9 (2%)	17 (3%)
Investigations	94 (6)	51 (4)	37 (7%)	28 (5%)
Nervous system disorders	40 (3)	30 (2)	10 (2%)	8 (1%)
SSTI Disorders	36 (2)	32 (3)	11 (2%)	22 (4%)

- Serious adverse event/deaths/other significant events

In all clinical studies, death occurred in 74/1474 patients in daptomycin group (5%) versus 24/1222 patients in the comparator groups (2%). However, in the cSSTI studies there were 8 deaths (1.5%) reported for each treatment and none was considered to be related to treatment.

Only 19 (<1%) patients had possibly or probably related SAEs (not including deaths), of which 16 received daptomycin. Within the population in the pivotal cSSTI studies there was little difference between daptomycin and comparative groups for rates of severe AEs.

Cardiac effects

Daptomycin-related cardiotoxicity was not observed in non-clinical studies.

There were 41 daptomycin-treated and 29 comparator-treated patients that experienced at least one AE consistent with cardiac rhythm disturbance. The applicant reviewed 31 cases (28 daptomycin and 8 comparators) for possible QT/QTc interval prolongation and/or pro-arrhythmic potential. Also, 39 cases (18 and 21 per treatment group) with other AEs associated with rhythm disturbances (e.g. tachycardia) were reviewed for possible ventricular events. There were three cases potentially indicative of an effect on ventricular repolarisation. In all cases it would appear that the most likely cause was the underlying disease, as daptomycin was continued and the ventricular arrhythmia continued after stopping daptomycin.

The effect of co-administration of daptomycin with drugs that interfere with calcium and/or potassium channels was explored. In the cSSTI studies, proportions with any cardiac AE while on a concomitant potassium ATPase channel antagonist were similar in the daptomycin- and comparator-treated groups (8 % and 7 %). For those on concomitant non-dihydropyridine calcium channel blockers the most frequent events were supraventricular rhythm disturbances but rates per treatment group were similar at 6% and 7%. For those on potassium channel antagonists, no cardiac events were reported from the cSSTI studies in daptomycin patients.

Overall based on the available data, it is unlikely that daptomycin when used to treat patients with cSSTI, is associated with a higher risk of cardiac AEs or peripheral vascular AEs nonetheless it cannot be ruled out a role of daptomycin given the background of other risk factors.

Effects on skeletal muscle

In the early studies of the 1980s, two of five healthy volunteers given daptomycin 4 mg/kg twice daily had muscle pain and weakness with rapid elevations in CPK at day 8. Both had some degree of

myoglobinaemia but daptomycin levels were within anticipated levels for healthy volunteers, symptoms resolved in 3-4 days and CPK values were near/normal within a week.

Across all the later studies with once daily dosing, most patients (71% daptomycin and 70% on comparators) had peak CPK levels <Upper Limit Normal (ULN). There were 12% and 11% in respective treatment groups with maximum values in the range ≥1 to <5 × ULN. However, 10 and 4 per group had values that reached ≥ 5 to < 10 x ULN while 16/1474 (1%) in the daptomycin group and 3/1222 (0.2%) that received comparators had levels that reached ≥ 10 x ULN. Nevertheless, most patients with CPK elevations did not have muscle related events (MREs). The incidence of myalgia and other MREs in subjects with normal CPK or levels <1000 U/L) were slightly higher in the daptomycin group. However, myalgia accompanied by CPK levels >10 x ULN only occurred in the daptomycin group. Of three subjects that fulfilled the criteria of clinically important myositis, two had high daptomycin exposures due to renal insufficiency. One of these had a CPK >10,000 U/L (from <100 U/L before hand) and two developed elevations >10 x ULN. Among those with CPK values >1000 U/L but <10 times ULN, a single case on daptomycin had a swollen arm and was classified as experiencing an MRE. There was no clear pattern of temporal relationship to therapy and in several cases the increases in CPK were thought likely due to concomitant procedures or underlying illness.

The data from literature, safety database and post-marketing do not suggest any additional effect on muscle when daptomycin is co-administered with other drugs that are recognised to induce myopathy. However the data are too limited to exclude such risk.

Peak CPK values *vs* $AUC_{0\text{-}inf}$ values were compared for symptomatic (with musculoskeletal events or weakness) and asymptomatic individuals but no correlation was observed between $AUC_{0\text{-}inf}$ and significantly elevated CPK levels (>5 × ULN; i.e. 1000 U/l) regardless of whether there were any symptoms.

Using the MedDRA SMQ plus the terms asthenia, pain in extremity, muscle atrophy and muscle tightness, there were around 80 post-marketing reports identified that contained at least one such AE. On applying the narrow search terms, 10/12 reports involved rhabdomyolysis, including one case reported as rhabdomyolysis and compartment syndrome. Of the 10 cases reported as rhabdomyolysis nine were known to have CPK values >10 × ULN and the other had an elevated CPK but with no specific value given. No serum or urinary myoglobin findings were reported for 7/10 while two were positive and one was negative. Five had some indication of renal impairment, two had a normal serum creatinine reported and there was no information for the other three.

Peripheral nerves

Following the identification of peripheral nerves as a potential target organ for daptomycin toxicity in animal studies, neurological monitoring was performed during the early clinical studies. Overall the risk of daptomycin induced neuropathy appears to be very low. Although rates of peripheral neuropathy and AEs that might reflect some neuropathic process have been similar in daptomycin and comparative groups, in some cases daptomycin might have been the cause and there has been a post-marketing case in which the true cause of the neuropathy has not been identified.

- Laboratory findings

Most of the laboratory abnormalities reported as AEs involved raised CPK (2% daptomycin and 1% comparators) or raised AST or ALT (1% - 2% per treatment group). The association between these has already been mentioned.

- Safety in special populations

Age

There were increases in most AE rates with age in both treatment groups but there was an overall higher total rates in the daptomycin group in pooled data from all studies. Some specific adverse events (e.g. related to system class cardiac, infections and infestations, metabolism and nutrition, respiratory, thoracic and mediastinal) occurred more commonly in daptomycin group over comparators. However, an analysis of AEs by age groups <65 years and ≥65 years that was restricted to patients who received 4 mg/kg per day daptomycin *vs* all comparator group patients did not demonstrate the above imbalances regarding cardiac, respiratory and metabolic AEs. These findings supported the assertion that some of the excesses of AEs seen in the daptomycin group among the elderly across all studies reflected sub-optimal therapy of infection that was, in many cases, due to inappropriately cautious dose adjustments being recommended in the protocol.

Safety of daptomycin in children and adolescent populations (< 18 years of age) has not yet been established.

Renal insufficiency

There was a trend for a higher incidence of AEs as renal clearance decreased although numbers with creatinine clearance < 30 ml/min were small. Apart from the patients with moderate renal impairment, this trend applied equally to daptomycin and comparator-treated patients.

When AEs were reviewed by renal function for the cSSTI studies it was again found that apart from the patients with moderate renal impairment the increase in AEs with decreasing function applied equally to daptomycin and comparator-treated patients. The incidence of AEs was higher in all and in elderly patients that had their daptomycin dose reduced and many of these were treatment failures.

The safety issues noted in clinical studies when CrCl fell below 30 ml/min are considered to be at least in part related to over-cautious dose adjustment. A clear relationship between renal insufficiency and AUC daptomycin and risk of raised CPK has not yet been demonstrated. Overall, there has been relatively little clinical exposure at the final agreed doses in clinical trials in the target indication.

Obesity

AEs were generally more common in obese subjects but there was no obvious relationship to daptomycin therapy.

- Discontinuation due to adverse events

Although 17% in the daptomycin group and 12% in the comparative group failed to complete study medication only 5% (67/1474) and 3% (36/1222), respectively, discontinued due to AEs. Among these, a raised CPK level led to discontinuation in eight and four per treatment group. Within the pivotal cSSTI studies, the rate of discontinuation due to AEs was the same (3%) in the two treatment groups and gastro-intestinal tract events predominated. A Kaplan-Meier analysis of the time to discontinuation due to AEs in cSSTI studies showed that over the recommended treatment duration of 7-14 days the probability of a patient discontinuing study treatment was very similar between treatment groups.

Post marketing experience

Since its launch (September 2003) to end of May 2005, it was estimated that over 83,000 patients might have been exposed to daptomycin in the US or Israel. There had been 431 AEs reported in 234 patients, including 76 reports that involved a total of 167 SAEs.

Elevated Transaminases: There had been 32 post-marketing reports of increased ALT, AST or transaminases or abnormal liver tests and four other reports were identified in which these events were not the primary focus but laboratory data were provided that indicated some abnormality of LFTs.

After review of the case details it was clear that a relationship with daptomycin could not be ruled out in a substantial number of reports. A proportion of transaminase elevations were also associated with CPK rises and muscle symptoms in some patients. These transaminase increases were considered to be likely to be due to skeletal muscle effects. The majority of the transaminase elevations were of Grade 1-3 toxicity and resolved upon discontinuation of treatment.

Blood creatinine increase: There were 26 reports of increased blood creatinine levels, renal failure, or creatinine renal clearance decreased. In half of the reports the relationship between treatment with daptomycin and creatinine elevations was questionable since blood creatinine later decreased despite continuation of daptomycin therapy or other causal factors were identified. Of 13 reports for which a relationship between daptomycin and increased creatinine levels could not be excluded most involved some confounding factors. There were nine cases for which a possible association with daptomycin was concluded.

Eosinophilia: Ten cases had been reported with a temporal association to daptomycin. Pulmonary eosinophilia has occurred.

Bone marrow toxicity: There were 8 cases of thrombocytopenia reported since US launch, of which 2 were diagnosed prior to starting daptomycin and 4 were associated with administration of heparin or warfarin. In 1 case there was temporal relationship between discontinuation of daptomycin and resolution of thrombocytopenia. There were also 9 cases of neutropenia, leucopenia or decreased WBC reported. Most cases involved confounding factors that could have contributed to the development of decreased WBC levels such as pre-existing neutropenia/low WBC, HIV, systemic lupus erythematosus, chemotherapy or concomitant medications.

International normalised ratio (INR) elevations: There have been some reports of patients (not on anticoagulants) who had apparent elevations in INR values without evidence of bleeding in temporal association with daptomycin therapy. Investigation, so far, have confirmed that daptomycin can interfere commercially available reagents used in determining the prothrombin time (PT) test in a concentration-dependent manner. Further studies are ongoing to further address this point and a warning has been included in the Summary of Product Characteristics.

5. Pharmacovigilance

Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

Risk Management Plan

A risk management plan was submitted.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. In addition the applicant undertook to specifically review the following adverse reactions and to report them in the PSUR according to the normal PSUR cycle using the International birth date of 12 September 2003:

- Muscle events
- Changes in daptomycin susceptibility
- Peripheral neuropathy and related terms
- Cardiac events
- Liver function abnormalities
- Effects on renal function
- Potential cases of drug-drug interactions due to protein binding
- Bone marrow toxicity
- Adverse events in patients with impaired renal function

A summary of the risk management plan for identified and potential risks associated with the use of daptomycin is summarised in the Table below:

Table 26: Summary of the risk management plan

Issue	Pharmacovigilance Action	Risk Minimisation Measures
Musculoskeletal	▪ Mechanism of action studies	Warning in the SPC to: • Measure plasma CPK at baseline and at regular intervals (at least once weekly) during therapy in all patients. • Monitor more frequently than once weekly patients with CPK > 5ULN at baseline, if daptomycin is given • Measure CPK more frequently than once weekly in patients who are at higher risk of developing myopathy. These patients include those with severe renal insufficiency (creatinine clearance < 30 ml/min) and patients taking other medications known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin). • Not administer daptomycin to patients who are taking other medications associated with myopathy unless it is considered that the benefit to the patient outweighs the risk. • Review regularly patients while on therapy for any signs or symptoms that might represent myopathy. • Have CPK levels monitored every 2 days for any patient that develops unexplained muscle pain, tenderness, weakness or cramps. • Discontinue daptomycin in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 ULN.
Patients with renal insufficiency	▪ Clinical trial ongoing in which the PK, efficacy and safety of daptomycin is evaluated in patients with CrCl < 50 ml/min ▪ Observational study in the elderly with cSSTI, including patients with moderate/severe renal insufficiency to provide more efficacy and safety data in clinical setting	Warnings in the SPC to: Monitor response to treatment and renal function in all patients with some degree of renal insufficiency (creatinine clearance < 80 ml/min) For patients with creatinine clearance < 30 ml/min and those on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). • To use daptomycin only if necessary • To closely monitor clinical response to treatment and renal function • To reduce Dose to 4 mg/kg administered as a single dose once every 48 hours
Elderly	▪ Observational study as above ▪ Collect safety data from a future clinical study in cSSTI comparing daptomycin to vancomycin	Warning in SPC to: ▪ To exercise caution if daptomycin is given to such patients.

	or teicoplanin	

6. Overall conclusions, benefit/risk assessment and recommendation

Quality

The active substance daptomycin is well characterised and documented. The pharmaceutical form selected, powder for concentrate for solution for infusion, is adequate taken into account the properties and the stability of the drug substance. The only excipient used is sodium hydroxide and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

The quality of CUBICIN is therefore considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the benefit-risk ratio.

Non-clinical pharmacology and toxicology

Daptomycin is a novel cyclic lipopeptide antimicrobial agent active against Gram-positive bacteria only.
Its mechanism of action is via binding followed by insertion in bacterial cell membranes resulting in rapid membrane depolarization and subsequent inhibition of protein, DNA and RNA synthesis. This is followed by bacterial cell death.
A range of safety pharmacology testings have been conducted and there was no evidence of potential effects on daptomycin on cardiovascular, respiratory, renal, gastrointestinal or immune systems.

Daptomycin presents a linear pharmacokinetics profile. It is predominantly plasma protein bound, and is not significantly metabolised. The majority of the administered dose is excreted via the kidney as unchanged. It does not induce or inhibit cytochrome P450 in the liver.
The toxic effects related to daptomycin were consistent across studies, regardless of changes in the excipients, formulations, and manufacturing processes during various stages of drug development.
Daptomycin administration was associated with minimal to mild degenerative/regenerative changes in skeletal muscle in the rat and dog, which occurred at exposure levels below human therapeutic levels. The myopathic effects were primarily related to time between doses and secondarily AUC, and were usually accompanied by elevations in CPK. No fibrosis or rhabdomyolysis was observed. All muscle effects, including microscopic changes, were reversible within 3 months following cessation of dosing. The mechanism has not been fully elucidated but seems to be link to a direct effect of daptomycin on skeletal muscle.
Effects on peripheral nerves were observed at higher doses than those associated with skeletal muscle effects in adult rats and dogs, and were primarily related to C_{max}. Peripheral nerve changes were characterised by minimal to slight axonal degeneration and were frequently accompanied by functional changes. Reversal of both the microscopic and functional effects was complete within 6 months post-dose. In the chronic studies, the no observed adverse effects level (NOAEL) in animal studies Cmax values were <5-fold human values at the recommended dose. The mechanism is unknown but the effect on skeletal muscle is independent of the effect on nerves.
In contrast to adult dogs, juvenile appeared to be more sensitive to peripheral effects of daptomycin.
Reproductive toxicity studies showed no evidence of effects on fertility, embryofoetal, or post-natal development. Nonetheless considering that daptomycin can cross the placenta of pregnant rats and in the absence of clinical data on pregnancies, daptomycin should not be used during pregnancy unless clearly needed as recommended in the SPC. Similarly in view of the lack of data of excretion of daptomycin in milk of lactating animals and in human, breastfeeding should be discontinued during treatment as mentioned in the SPC. Daptomycin was not mutagenic or clastogenic. Considering the

expected short duration of treatment with daptomycin (less than 6 months) the lack of carcinogenicity is acceptable in accordance with the current international guidelines on carcinogenicity testing.

Clinical data

Daptomycin has linear kinetics over a dose range up to 8 mg/kg and distributes rapidly in the plasma and to more highly vascularised organs. Approximately 90 % is bound to plasma proteins. It is cleared by the kidneys mainly as unchanged drug with minimal to no active tubular secretion of daptomycin. Caution is recommended when co-administered with products known to reduce renal filtration.
Daptomycin does not undergo significant metabolism. It is not an inducer or inhibitor of CYP450 and the potential for pharmacokinetic interaction is low.

Renal insufficiency is associated with reduced daptomycin clearance and increased systemic exposure. In subjects with severe renal insufficiency (CLcr<30ml/min) and end-stage renal disease, exposure (AUC) and elimination half life are increased between 2-3-fold relative to healthy subjects. Dose interval adjustment is therefore needed. The recommendations in the SPC are based on modelling and have not been clinically evaluated. Therefore, such patients should only be treated if needed and clinical response to treatment and renal function should be closely monitored. In addition, although no adjustment is recommended for those patients with creatinine clearance >30ml/min, monitoring of renal function and treatment effect is required due to the paucity of clinical data. No dose adjustment is necessary when administering daptomycin in patients with moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency (Child-Pugh C classification) have not been evaluated and therefore the Summary of Product Characteristics recommends caution when daptomycin is used in these patients. In the elderly, no dose adjustment is required unless there is severe renal insufficiency.
Although in obese and very obese patients the systemic exposure increased, no dose adjustment is warranted.

Daptomycin exhibits rapid, concentration dependent bactericidal activity against sensitive Gram-positive organisms *in vitro*. In animal models AUC/MIC and Cmax/MIC correlate with efficacy and predicted bacterial kill *in vivo* at single doses equivalent to human doses of 4mg/kg once daily.
Breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and streptococci (except *S. pneumoniae*) are Susceptible $\leq$ 1 mg/l and Resistant > 1 mg/l. Resistant pathogens have been rarely recovered from patients treated with CUBICIN. Emergent decreases in susceptibility have been observed with daptomycin in patients with difficult to treat infections and/or for prolonged periods.

The demonstration of efficacy of daptomycin in cSSTI due to Gram-positive bacteria is based on 2 investigator-blinded, randomised, multicentre studies against vancomycin or semi-synthetic penicillins: Study 9801 in which 547 subjects were randomised and study 99-01 in which 571 were randomised.

In study 9801 the clinical response at test of cure (cure and clinical improvement) was 140/209 (67 %) in the daptomycin group compared to 142/212 (67 %) in the comparator (95 % CI – 9.0; 9.0) in the modified-to-treat population.
In study 9901, the clinical response at test of cure (cure and clinical improvement) was 180/213 (84.5%) in the daptomycin group compared to 214/255 (83.9 %) in the comparator (95 % CI – 7.2; 6.0) in the modified-to-treat population. The demonstration of the non-inferiority of daptomycin compared to vancomycin or semi-synthetic penicillins was supported by further subgroup analyses.
There were no major differences between outcomes in patients with severe and non-severe infections who were treated with daptomycin. Nonetheless the limitations in the characteristics and severity of the infection enrolled have been reflected in the Summary of Product Characteristics: 36 % of patients treated with daptomycin met the criteria for systemic inflammatory response syndrome (SIRS). The most common type of infection treated was wound infection (38% of patients) while 21 % had major abscesses. There is also limited experience in treating patients with concurrent bacteraemia (less than 3 % of patients treated with daptomycin for complicated skin and soft tissues infections had a bacteraemia) as this was an exclusion criterion for entry into the clinical trials. Therefore the use of

daptomycin in such patients is not recommended as reflected in the Summary of Product Characteristics.

There is insufficient evidence of daptomycin's clinical effect against *Enterococcus faecalis* and *Enterococcus faecium*.

Safety

In clinical trials more than 1400 subjects have received daptomycin. Overall 20 % in the daptomycin compared to 19 % in the comparator group had an adverse event considered to be possibly or probably related to treatment. The commonest adverse reactions reported with daptomycin were headache, nausea, vomiting, diarrhoea, muscle pain, fungal infections, rash, infusion site reaction, increased CPK and abnormal liver enzymes. As in preclinical studies, one of the risks associated with the use of daptomycin is musculoskeletal events and occasionally myopathy. Recommendations on the monitoring of CPK have been included in the Summary of Product Characteristics and further investigation into the mechanism of action of the effect will be conducted**.** Although peripheral nerves have been identified as target organs in toxicity studies, in clinical studies, this has been reported uncommonly. Nonetheless this will be specifically review and report in the PSUR:

The safety database has been substantiated by data from post-marketing use in the US and Israel (estimated over 83,000 patients exposed to daptomycin). All the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Benefit/risk assessment

Overall the efficacy data were considered sufficient to support an indication for use in cSSTI due to Gram-positive bacteria in adults.
Certain limitations in the data that support the efficacy of daptomycin have been reflected in the SPC. Based on the safety data, a number of potential risks associated with the use of daptomycin have been identified. A risk management plan was submitted and includes agreed pharmacovigilance activities to further define the safety profile post-authorisation. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information. The applicant also undertook to gather further data post-authorisation. In particular the applicant will provide further efficacy and safety in elderly patients and patients with renal insufficiency mainly through an observational study of cSSTI and a planned randomised controlled study in cSSTI**.** The applicant undertook to provide annually reports on the susceptibility of clinically obtained Gram-positive isolates to daptomycin in European medical centres and to further explore the mechanism of resistance.
Safety and efficacy in children and adolescents has not yet been established but the applicant undertook to submit results of planed studies as part of the follow-up measures to be fulfilled post-authorisation.

Recommendation

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).