comparator subjects in these studies. In Phase III cSSSI and CAP studies 7/989 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In animals, effects of daptomycin on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving Cubicin." Since peripheral neuropathy characterized by axonal degeneration were observed in adult dogs and monkeys, this paragraph was added to provide the practitioner with all available clinical experience with neuropathy in human studies.

GERIATRIC USE

- The following sentence was added to the demographic information and efficacy data to complete the characterization of daptomycin in the geriatric population. "In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age in both cSSSI studies."

ADVERSE EVENTS

- The second paragraph was modified to read "Clinical studies sponsored by Cubist enrolled 1,409 patients treated with daptomycin and 1,185 treated with comparator. Most adverse events reported in these clinical studies were described as mild or moderate in intensity. In Phase III cSSSI trials, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients." These changes were made to modify language to include AEs of severe intensity as well as to more accurately reflect the discontinuation rate due to AEs.
- The following paragraph was added in order to provide practitioners information regarding the adverse event profile of daptomycin in the treatment of CAP, as well as the cause: " In Phase III studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**)
- The sentence

  " was deleted from this section. A more complete summary of the Lilly and Cubist experience with neuropathy is now included in PRECAUTIONS.

- Under Laboratory Changes: The FDA proposed changes in the **ADVERSE EVENTS** section include the addition of a table (Table 6) showing rates of various degrees of CPK elevation in daptomycin and comparator-treated patients in cSSSI studies.

  This table provides information to prescribers on the relative rates of CPK elevation in the population of patients for whom daptomycin is indicated, and illustrates that extreme elevations of CPK consistent with myopathy occur in daptomycin-treated patients, although at a low rate In this context, it is important to note that the reported incidence of statin-associated myopathy (2.3 per 10,000 person-years [Epidemiology 2001;12:565-9] is lower than the corresponding incidence reported in Phase III trials for daptomycin (0.2%).

DOSAGE AND ADMINISTRATION

- The following was added to the first paragraph under "Complicated Skin and Skin Structure Infections": "Doses of daptomycin higher than 4 mg/kg/day have not been studied in Phase III controlled clinical trials. In Phase I and 2 clinical studies, CPK elevations appeared to be more frequent when daptomycin was dosed more frequently than once daily. Therefore, daptomycin should not be dosed more frequently than once a day." The sentence regarding dosing was added to provide practitioners who may be considering off-label use at a higher dose than 4 mg/kg q 24h that safety data to support such use has not yet been collected. The sentence regarding frequency of dosing was added to reflect that in a Phase I dose-escalation study (Study B8B-MC-AVAP) conducted by Lilly daptomycin at 4 mg/kg q12h for 14 days was administered to five normal subjects. At about Day 8 of treatment, two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK. Study medication was discontinued and the effects resolved within a few days without sequelae. Subsequent animal studies indicated that for a given level of drug exposure the frequency and severity of skeletal muscle toxicity were decreased with once daily dosing compared with divided doses.

D. Dosing

Daptomycin exhibits concentration-dependent bactericidal activity *in vitro* against the claimed Gram-positive organisms. No formal dose response or concentration response study was performed by Cubist. The recommended daptomycin dosage regimen is based on clinical experience in the primary comparative studies, and on

microbiological and pharmacokinetic considerations. The primary comparative studies in complicated skin and skin structure infections were each performed using a daptomycin regimen of 4 mg/kg intravenously q24h for 7 to 14 days. The two studies of daptomycin in community acquired pneumonia also used a dose of 4 mg/kg q 24h for 5-14 days; this data was submitted to the NDA in support of safety.

In a multicenter Phase II trial, daptomycin (2 mg/kg q24h) was as effective as conventional therapy (oxacillin, vancomycin, penicillin, or ampicillin plus an aminoglycoside) in the treatment of Gram-positive skin and soft tissue infections. Thirty (96.8%) of 31 evaluable subjects treated with daptomycin had a favorable response, compared to 41/43 (95.3%) of the evaluable subjects who received conventional therapy. Bacteriological eradication was observed in 30/31 (96.8%) daptomycin-treated subjects, compared with 34/43 (79.1%) of subjects treated with conventional therapy. Daptomycin was effective against a variety of infecting pathogens, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, other species of streptococci, and enterococci. In this study, daptomycin at 2 mg/kg q24h was less effective than conventional therapy in the treatment of bacteremia. In a subsequent Phase II trial in which daptomycin dose was increased to 3 mg/kg q12h, a successful clinical and bacteriologic outcome was seen in 21/24 (87.5%) subjects with bacteremia treated with daptomycin. This result was similar to the percentage of favorable outcomes for conventional therapy in both Phase II studies (8/9 [88.9%] in the first study and 3/4 [75.0%] in the second study).

In studies conducted to date by Lilly and Cubist, the incidence of CPK elevations does not appear to be dose-related. In Phase I and 2 clinical studies, CPK elevations did appear to be more frequent when daptomycin was dosed more frequently than once daily. In a Phase I dose-escalation study (Study B8B-MC-AVAP) conducted by Lilly, daptomycin at 4 mg/kg q12h for 14 days was administered to five normal subjects. At about Day 8 of treatment, two of the five subjects experienced muscle pain and weakness as well as rapid elevations in CPK. Study medication was discontinued and the effects resolved within a few days without sequelae. Subsequent animal studies indicated that for a given level of drug exposure the frequency and severity of skeletal muscle toxicity were decreased with once daily dosing compared with divided doses. Therefore, when Cubist acquired the drug for development, the choice was made to use only single daily dosing.

In Phase II clinical trials conducted by Eli Lilly and company and by Cubist, daptomycin was administered at 2, 4, and 6 mg/kg q24h and at 3 mg/kg q12h to 349 patients with a variety of serious infections due to Gram-positive organisms, including bacteremia, endocarditis, skin and soft tissue infection, and pneumonia. In these studies, the incidence and nature of adverse events associated with daptomycin were comparable to that seen with conventional therapy. In Cubist sponsored Phase II/III studies, 70 patients received the proposed dose of 4 mg/kg q 24h.

Conclusions

- There is adequate efficacy and safety data to recommend approval of daptomycin 4 mg/kg/day intravenously for 7-14 days, in patients 18 years of age or older, with complicated skin and skin structure infections due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*.

- Sufficient numbers of patients with complicated skin and skin structure infections such as major abscesses, infected ulcers, wound infections, and cellulitis were included in the studies to justify inclusion in the label.

- Data were inadequate to include patients with infected diabetic ulcers.

- Gastrointestinal disorders such as nausea, constipation, diarrhea, and vomiting were the most common adverse events reported in Phase III cSSSI studies. The rates of overall adverse events, deaths, serious adverse events other than death, and adverse events leading to discontinuation were similar in both treatment groups.

- One daptomycin treated patient had biochemical and clinical evidence of myopathy while on therapy.

- There was no clinical or laboratory evidence for daptomycin cardiotoxicity in pre-clinical studies or in Phase I, II, and III data.

- There was no clinical or laboratory evidence for daptomycin hepatotoxicity in pre-clinical studies or in Phase I, II, and III data.

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MEDICAL OFFICER

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