CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Pharmacology Review(s)

Note:

This will be the Standard CDER Coversheet

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: Approval with appropriate warnings and caveats in the label.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendations on labeling:
An insertion to the precautions section on the non-clinical findings of muscular and neurologic toxicity is recommended. Minor changes to the distribution, pregnancy and animal toxicology sections are also requested.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings:
The major target organs of toxicity in rat, dog and monkey were muscle and peripheral nerves. Muscle damage consisted of muscle degeneration/regeneration and usually resolved within 1 month of cessation of treatment. Muscle changes were sometime accompanied by increases in CPK. Peripheral nerve damage occurred at higher doses and included loss of patellar/gag reflexes, loss of pain perception, decreases in nerve conduction velocity, and axonal degeneration. Recovery was dependent on dose, and was incomplete after a 3 month period. In the rat, renal toxicity was also observed. The NOEL levels from the animal toxicity studies, when expressed as either AUC or doses on a body surface area basis, were less than those at the proposed human dose of 4 mg/kg. Similar toxicities were noted in the 1, 3 and 6 month toxicity studies.

Daptomycin was negative in the Segment I, II and III reproductive toxicity studies. Daptomycin was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* genotoxicity tests.

2.2 Pharmacologic activity:
The proposed mechanism of action is through interaction with the bacterial membrane via the fatty acid chain. A calcium dependent insertion occurs, the membrane potential decreases, and the cell dies.

2.3 Nonclinical safety issues relevant to clinical use:
Muscle and peripheral nerve damage were seen in all species tested as shown by changes in clinical signs and microscopic changes. In human trials, muscle weakness was observed. In animals, the no-observed effect levels (NOELs) were at or below those in the proposed human doses on both an AUC and body surface area basis. Muscle damage occurred at lower doses than neurologic changes, and

resolved within several weeks of the cessation of dosing. At higher doses, peripheral nerve damage was still present 3 months after the recovery period. Both muscle and nerve damage could occur after a single dose of daptomycin. While severe muscle and neurologic damage was accompanied by >10 fold elevations in CPK, lesser damage did not correlate well with elevations in CPK either in frequency or magnitude.

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