CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

DAPTOMYCIN
(Cubicin® – Oryx Pharmaceuticals Inc.)

Description:
Daptomycin is a parenteral cyclic lipopeptide antimicrobial agent with bactericidal properties against Gram positive organisms including methicillin resistant *Staphylococcus aureus (S. aureus)*. It is approved for the treatment of complicated skin and skin structure infections and *S. aureus* bloodstream infections, including those with *S. aureus* right-sided infective endocarditis.

Dosage Forms:
500 mg/10 mL vial. The recommended dose for the treatment of complicated skin and skin structure infections is 4 mg/kg once every 24 hours. A dose of 6 mg/kg once every 24 hours is recommended for *S. aureus* bacteremia, including those with right-sided infective endocarditis.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that daptomycin not be listed.

Reasons for the Recommendation:
1. Based on the results of three open-label randomized controlled trials (RCTs) (designed as non-inferiority trials), the Committee felt that there was no therapeutic advantage of daptomycin as a first-line agent over other antimicrobial agents. Moreover, the Committee had concerns with the design, conduct and reporting of these trials (e.g. open-label design, large number of patients pre-treated with vancomycin, amendment to trial protocol that was initially designed to evaluate right-sided infective endocarditis).

2. The Committee considered whether daptomycin should be listed for patients with a vancomycin resistant *S. aureus* strain or with intolerance to vancomycin, but this population has not been evaluated in RCTs.

3. The Committee had concerns about potential resistance to daptomycin. In an endocarditis/bacteremia trial, six of the 19 patients (32%) with microbiological failure to daptomycin developed reduced susceptibility to daptomycin during the course of therapy.

4. The safety of daptomycin in patients with renal impairment has not been established.

5. Daily drug costs for daptomycin are similar to, or higher than comparator agents.

Summary of Committee Considerations:

The Committee considered the results of two systematic reviews of RCTs of daptomycin, one in patients with *S. aureus* bacteremia and one in patients with complicated skin and skin structure infections. One trial in an intention-to-treat (ITT) population of 235 patients with *S. aureus* bacteremia / right-sided infective endocarditis that compared daptomycin with a mixed comparator arm (vancomycin or one of the four semi-synthetic penicillins: nafcillin, oxacillin, cloxacillin, flucloxacillin) and gentamicin met the eligibility criteria for the first systematic review. Two identically-designed trials in a total ITT population of 899 patients were included in the second systematic review of complicated skin and skin structure infections. These two open-label, non-inferiority RCTs compared the efficacy of daptomycin with a mixed comparator arm (vancomycin or a semi-synthetic penicillin) in treating *S. aureus* infections. Concomitant antimicrobial therapy was permitted in both treatment arms of these two trials. The primary outcome of all three trials was a composite outcome of clinical success evaluated at the end of therapy and at 42 days post-therapy for the bacteremia/endocarditis trial or at 6-20 days post-therapy in patients with complicated skin and skin structure infections.

Results from the bacteremia/endocarditis trial showed a similar clinical success at 42 days post-treatment for patients who received daptomycin (44.2%) versus those in the comparator arm (41.7%). Of the 19 patients with microbiological failures to daptomycin, six (32%) developed reduced susceptibility to daptomycin during the course of therapy.

Both open-label trials in complicated skin and skin structure infections showed that daptomycin was non-inferior to the mixed comparator arm in terms of clinical success rates although success rates of daptomycin differed substantially between the two trials (65% and 84%).

Daptomycin is associated with myositis, which requires monitoring of creatine kinase for patients on therapy.

The daily drug cost of daptomycin is $165, which is greater than generic vancomycin (2 g, $92.54), generic cloxacillin (1-8 g, $0.70-$14.40) and linezolid (1200 mg, $141.28) but similar to tigecycline (100 mg, $165.46).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. To date, there have been no clinical isolates of vancomycin-resistant *S. aureus* in Canada.

3. The Committee considered linezolid as a comparator for complicated skin and skin structure infections. The product monograph for linezolid includes a warning on a mortality imbalance in a bacteremia trial which is still under evaluation. However, this warning was based on the group of patients with Gram negative infections, or with no pathogen identified at baseline.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the

Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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