[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 2 JANUARY 2024.]

Daptomycin and linezolid

for treating vancomycin-resistant enterococci bloodstream infections

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Linezolid 600 mg tablet and 2 mg/ml solution for infusion for treating patients with culture-positive vancomycin-resistant enterococci (VRE) bloodstream infections.

Subsidy status

Linezolid 600 mg tablet and 2 mg/ml solution for infusion are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

Treatment with linezolid should be initiated and monitored by an infectious disease specialist.

MAF assistance **does not** apply to any other non-bloodstream culture-positive VRE infections treated with linezolid.

MAF assistance **does not** apply to daptomycin 500 mg vial.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of daptomycin and linezolid for treating vancomycin-resistant enterococci (VRE) bloodstream infections. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical evidence for linezolid and daptomycin was used to inform the evaluation. The Committee acknowledged that only linezolid has HSA registration for treating VRE infections, and using daptomycin for this indication was 'off-label' in Singapore and in other jurisdictions.

1.2 The Committee was reminded that subsidy consideration for off-label use of HSA-registered drugs was permissible if all these conditions were met:

- There is sufficient evidence available to assess the safety, efficacy, and cost-effectiveness of the off-label use of the drug;
- The off-label use of the drug is the current standard of care in local clinical practice and also in line with international best practice; and
- There is a lack of affordable and cost-effective treatment alternatives to the off-label drug.

1.3 The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money)—the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1 The Committee noted that in local clinical practice, daptomycin (off-label) and linezolid (HSA-registered) are reserved for treating patients who are unable to receive vancomycin or with VRE infections, in line with international clinical practice guidelines.

2.2 The Committee acknowledged effective treatment for VRE infections represents an important gap in the current list of subsidised antibiotics. Therefore, there was an unmet clinical need to provide a subsidised treatment option for these patients.

2.3 The Committee noted that linezolid has an oral formulation that allows haemodynamically stable patients to complete their treatment course without requiring further hospitalisation.

Clinical effectiveness and safety

3.1 The Committee acknowledged the evidence that informed the evaluation was from small retrospective cohort studies of low to moderate quality, predominantly in patients with VRE bloodstream infections. The Committee noted considerable variations in findings on the effectiveness of daptomycin and linezolid for treating VRE.

3.2 Nonetheless, the Committee considered that daptomycin and linezolid were generally comparable with regards to safety and efficacy for VRE bloodstream infections. This view was also consistent with local clinicians' experience of these antibiotics.

3.3 The Committee noted from meta-analyses that no cases of elevated creatinine phosphokinase with daptomycin use, or cases of thrombocytopenia or serotonin syndrome caused by significant drug interactions with linezolid were highlighted.

Cost effectiveness

4.1 The Committee noted that no published local or overseas economic evaluations were available. The Committee agreed a cost-minimisation approach was appropriate to choose the agent with the lowest cost for subsidy in view of comparable clinical efficacy. On this basis, linezolid infusion was considered to be the preferred agent given its lower daily cost price compared to daptomycin infusion. In patients suitable for oral treatment, the generic linezolid tablet was considered the most cost-effective treatment option.

Estimated annual technology cost

5.1 The Committee estimated around 40 people with proven VRE bloodstream infections in Singapore would benefit from government assistance for linezolid or daptomycin. The annual cost impact was estimated to be less than SG$500,000 in the first year of listing on the MAF.

Additional considerations

6.1 The Committee considered whether subsidy should be extended to other VRE infections, such as urinary tract infections and abscesses. They acknowledged that evidence in non-bloodstream VRE infections was lacking, hence it was unclear whether the efficacy and safety of daptomycin and linezolid seen in patients with bloodstream infections was generalisable to other conditions. As such, they were unable to recommend subsidy of either agent for treating non-bloodstream VRE infections.

Recommendation

7.1 Based on available evidence, the Committee recommended linezolid 600 mg tablet and 2 mg/ml solution for infusion be listed on the MAF for treating culture-positive VRE bloodstream infections, in view of the clinical need to provide patients with a subsidised treatment option.