# Scottish Medicines Consortium

## daptomycin 350mg powder for concentrate for solution for infusion (Cubicin®)

## Chiron Corporation Limited No. (248/06)

10 March 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Daptomycin (Cubicin®)** is accepted for restricted use within NHS Scotland for the treatment of complicated skin and soft tissue infections in adults.

Daptomycin should be restricted to use in patients with known or suspected *methicillin-resistant Staphylococcus aureus* (MRSA) infection and on the advice of local microbiologists or specialists in infectious disease.

Daptomycin has a higher acquisition cost than some alternative treatments; it does not, however, require therapeutic drug monitoring.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

**daptomycin 350mg powder for concentrate for solution for infusion (Cubicin®)**

## Indication

For the treatment of complicated skin and soft-tissue infections in adults. Daptomycin is active against Gram-positive bacteria only. In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, it should be co-administered with appropriate antibacterial agents.

## Dosing information

4mg/kg by intravenous infusion once every 24 hours for 7-14 days or until the infection has resolved.

## UK launch date

1st March 2006

## Comparator medications

Other antibacterials with activity against Gram-positive bacteria. Flucloxacillin is likely to be one of the first line agents for uncomplicated infections. Comparators for complicated infections are likely to include vancomycin, teicoplanin, linezolid and quinupristin/dalfopristin.

## Cost of relevant comparators

| Drug | Dose | Daily Cost (BNF 50th edition) | Cost for 10 day course |
|---|---|---|---|
| **Daptomycin** | **4mg/kg daily (IV)** | **£62*** | **£620*** |
| Teicoplanin | 400mg initially then 200mg daily (IV/IM) | £36 400mg stat<br>£18 200mg daily | £194 |
| Vancomycin | 1gram twice daily (IV) | £32 | £322 |
| Linezolid | 600mg twice daily (orally or IV) | £89 | £890 |
| Quinupristin/dalfopristin | 7.5mg/kg 8 hourly (IV) | £111** | £1110** |

*based on use of one vial 350mg which is suitable for adults <88kg.

** based on use of one vial 500mg which is suitable for adults <67kg. For patients weighing >67kg, the number of vials and cost doubles.

Note: reduced contract prices may be available in hospital.

## Summary of evidence on comparative efficacy

Daptomycin is the first of a new class of antibacterials, the cyclic lipopeptides, which is active against Gram-positive bacteria only. Commonly susceptible organisms include *Staphylococcus aureus*, *Staphylococcus haemolyticus*, coagulase negative staphylococci, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus pyogenes*, Group G streptococci, *Clostridium perfringens* and *Peptostreptococcus spp*. It offers a unique site and mechanism of action through calcium-dependent binding to bacterial membranes of both growing and stationary phase cells. This causes depolarisation, leading to rapid inhibition of protein, DNA and RNA synthesis and bacterial cell death with negligible cell lysis.

Daptomycin has been approved in Europe for the treatment of complicated skin and soft tissue infections. Such an infection is considered complicated if it involves deeper skin structures (e.g. fascia or muscle layers), needs significant surgical invention, or arises in the presence of significant co-morbidities (e.g. diabetes mellitus or HIV infection).

The key data to support the use of daptomycin for complicated skin and soft tissue infections come from the results of two randomised, investigator-blinded, non-inferiority studies. One was conducted in the United States and South Africa; the other in Europe, South Africa, Australia and Israel. Published results are only available as a combined analysis. Both studies had essentially the same design and enrolled patients with a primary diagnosis of a complicated skin or soft tissue infection thought to be due, at least in part, to a gram-positive organism who required hospitalisation and parenteral antibacterial therapy for at least 96 hours. Based on assessment of the patient's infection severity and likelihood of infection with MRSA, the investigator assigned the comparator (penicillinase-resistant penicillin or vancomycin) before randomisation. Patients with severe disease or suspected MRSA would receive vancomycin as the comparator. Patients were then randomised to receive daptomycin (4mg/kg IV daily) or the pre-chosen comparator: penicillinase-resistant penicillin (cloxacillin, nafcillin, oxacillin or flucloxacillin 4-12g IV daily in equally divided doses) or vancomycin (1g IV 12 hourly) for 7-14 days. Concomitant aztreonam and/or metronidazole was administered to 24% and 27% of daptomycin- and comparator-treated patients respectively. Ancillary surgical procedures (e.g. incision and drainage or wound debridement) were also performed in 29% of patients in each group.

The primary endpoint was the rate of clinical success, defined as the resolution of signs and symptoms so that no further antibiotic therapy was required at the test-of-cure assessment (6-20 days post treatment). In the modified intention-to-treat population (all patients with an infection who received at least one dose of study medication and had a gram-positive organism isolated at baseline), clinical success was achieved in 75% of both daptomycin- and comparator-treated patients. Rates of clinical success were also similar between the daptomycin and comparator groups when assessed by the baseline diagnosis: wound infection 84% vs 87%, major abscess 92% vs 88%, infected ulcer (diabetic) 66% vs 70% and infected ulcer(non diabetic) 79% vs 83% and by the infecting organism. Non-inferiority was demonstrated.

Results were also presented for clinical success rates for the clinically evaluable population according to the class of comparator assigned pre-randomisation. For patients pre-assigned to penicillinase-resistant penicillin, clinical success was achieved in 87% of daptomycin-treated and 91% of comparator-treated patients (95% CI for difference: -1.9 to 8.3). For patients pre-assigned to vancomycin, clinical success was achieved in 81% of daptomycin-treated and 74% of comparator-treated patients (95% CI for difference: -17 to 2.9).

A separate publication has reported pooled results from the above studies for the subgroup of patients with infected diabetic foot ulcers. Of the 1092 patients enrolled in the original two studies, 133 had an infected diabetic ulcer and 103 were clinically evaluable (daptomycin, n=47 and comparator, n=56). In the clinically evaluable population, the clinical success rates were 66% and 70% respectively.

## Summary of evidence on comparative safety

In pooled data from the two studies, described previously, the frequency and distribution of adverse events were similar in both treatment groups. At least one adverse event, considered to be related to study treatment, was reported in 18% of daptomycin- and 21% of comparator-treated patients, with severe adverse events reported in 11% and 9% of patients in these groups, respectively. Treatment discontinuation due to adverse events occurred in 2.8% of patients in both groups.

Daptomycin has been reported to have the potential for muscle toxicity and therefore CK levels were monitored closely during the studies. However, there was no significant difference in the frequency of abnormal CK levels between the groups. Elevated levels were reported as treatment related in 2.1% of daptomycin treated patients and 1.4% of comparator treated patients. The draft summary of product characteristics for daptomycin provides advice for monitoring these levels during treatment.

## Summary of clinical effectiveness issues

The clinical studies described above have demonstrated non-inferiority to the comparators used (cloxacillin, nafcillin, oxacillin, flucloxacillin and vancomycin). In Scottish practice, the likely comparators for such infections would be flucloxacillin for sensitive organisms, with vancomycin or teicoplanin for serious infections (e.g. MRSA) and linezolid or quinupristin/dalfopristin reserved for infections resistant to these antibiotics. In initial practice, daptomycin is most likely to compete with the latter group of drugs. As with other new antibacterials, in order to maintain efficacy and prevent or delay the appearance of resistant strains, it should be used prudently. There are no directly comparative clinical data comparing daptomycin with linezolid or quinupristin/dalfopristin.

The numbers of individual types of infections treated were relatively limited: 44% of patients had a wound infection, 24% a major abscess, 12% infected diabetic ulcers and 13% infected non-diabetic ulcers. The number of patients in the studies with MRSA was also small (9.7%). These factors may affect the extrapolation of the trial results in terms of clinical success in the studies into practice.

## Summary of comparative health economic evidence

A cost-minimisation analysis was submitted comparing vancomycin to daptomycin as first-line therapy for patients with suspected or confirmed MRSA skin or soft tissue infections. Patients who failed first-line vancomycin therapy were given either linezolid or daptomycin. Patients failing first-line daptomycin therapy were given teicoplanin, linezolid or vancomycin. The comparators were appropriate and reflect Scottish clinical practice.

It was appropriate to use a cost-minimisation approach because the submitted clinical evidence demonstrated the equivalent efficacy of daptomycin and vancomycin. The economic evaluation assumed equal efficacy and equal treatment duration for daptomycin and

vancomycin. Adverse events, drop-outs and other drug administration costs (except antibiotic level and CK monitoring) were also assumed to be equal for both drugs.

Data sources for the economic evaluation were manufacturer (drug cost of daptomycin), BNF (all other drug costs), NHS provider tariffs (antibiotic level and CK monitoring), ISD Scottish Health Care Cost Book (inpatient stay). Clinical evidence used in the economic evaluation came from the pooled analysis of the two clinical studies and a published randomised control trial for linezolid.

Baseline results suggest that daptomycin offers cost-savings of £25 per patient, the higher drug acquisition cost of daptomycin being offset by lower monitoring costs. The cost saving of £25 per patient is based on the assumption that there are two vancomycin serum tests per day per patient. The sensitivity analyses demonstrated the robustness of the results. The key variable that the results were sensitive to was the number of vancomycin serum level monitoring tests. The break-even point at which daptomycin is cost neutral to vancomycin is 1.7 serum tests per day.

The economic evaluation demonstrated that daptomycin is an alternative to vancomycin for patients with suspected or confirmed MRSA skin or soft tissue infections. The cost savings projected are dependent on the number of vancomycin serum monitoring tests and may not be realised in practice. No economic evidence was submitted for patients with less resistant staphylococcal infections or mixed infections (gram-negative and/or anaerobic bacteria).

## Patient and public involvement

A Patient Interest Group Submission was not made.

## Budget impact

The manufacturer estimated the eligible patient population at 2,083 patients per annum. Market share was projected to rise from 3% in year 1 to 21% in year 5. Additional drug costs, resource savings, and the consequent net budget savings were presented for years 1 to 5. However, this assumed a resource saving per patient of £25, which will not necessarily be realised.

## Additional information

In the early 1990s, the clinical development of daptomycin (administered every 12 hours) was suspended because of dose-dependent toxicity in the form of elevated CK. Use of the proposed dose (4mg/kg daily) has demonstrated preserved clinical efficacy and minimal toxicity.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 28 February 2006.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.*

*Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38(12):1673-81.*

*Lipsky BA, Stoutenburgh U. Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. J Antimicrob Chemother 2005;55(2):240-5.*

*Raghavan M, Linden PK. Newer treatment options for skin and soft tissue infections. Drugs 2004; 64: 1621-42.*