Scottish Medicines Consortium

daptomycin, 350mg and 500mg vials of powder for solution for infusion (Cubicin®) No. (449/08)

Novartis Pharmaceuticals UK Limited

11 February 2008

The Scottish Medicines Consortium 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 *Staphylococcus aureus* bacteraemia (SAB) when associated with right-sided infective endocarditis (RIE) or with complicated skin and soft-tissue infections in adults.

Daptomycin should be restricted to use in patients with known or suspected methicillin-resistant *S. aureus* (MRSA) infection and on the advice of local microbiologists or specialists in infectious disease. Daptomycin has been shown to be as effective as standard therapy in patients with *S. aureus* bacteraemia with or without endocarditis, though data on the subgroup of patients with RIE due to MRSA are very limited.

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

Indication

For the treatment of *Staphylococcus aureus* bacteraemia (SAB) when associated with right-sided infective endocarditis (RIE) or with complicated skin and soft-tissue infections (cSSTI) in adults.

Dosing information

The recommended dose is 6mg/kg administered by intravenous infusion once every 24 hours. In patients with SAB-RIE, the duration of therapy should be in accordance with available official recommendations. In patients with SAB-cSSTI, the duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.

Product availability date

September 2007

Summary of evidence on comparative efficacy

Daptomycin is a cyclic lipopeptide active against Gram-positive bacteria only. It has a unique site and mechanism of action through calcium-dependent binding to bacterial membranes in 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 was launched in March 2006 for the treatment of cSSTI in adults. This submission relates to the new indication for the treatment of SAB-RIE and SAB-cSSTI.

The pivotal study supporting this indication was an open-label, randomised, non-inferiority study in 246 patients with *S. aureus* bacteraemia with or without endocarditis. Eligible patients were aged $\geq$ 18 years and had at least one blood culture positive for *S. aureus* within two days prior to starting therapy. The investigator made a baseline diagnosis according to modified Duke criteria. An independent adjudication committee, blinded to treatment allocation, made the final diagnosis and assessed the outcomes. Patients were randomised, in a 1:1 ratio stratified by investigative site, to receive daptomycin (6mg/kg daily) or standard therapy. Depending on the methicillin susceptibility of the infecting organism, patients in the standard therapy arm received either anti-staphylococcal penicillin (nafcillin, oxacillin or flucloxacillin at a dose of 2g every 4 hours) for *methicillin-sensitive S. aureus* (MSSA) or vancomycin (1g every 12 hours with appropriate dose adjustment) for MRSA. Gentamicin (1mg/kg every 8 hours) was given to all patients in the standard therapy arm and daptomycin-treated patients who had left-sided infective endocarditis (LIE).

Treatment duration was based on the diagnosis as determined by the investigator and the susceptibility of the *S. aureus* isolate. The minimum duration of therapy was 10 days for uncomplicated bacteraemia, 14 days for uncomplicated MSSA RIE and 28 days for complicated bacteraemia,or complicated RIE and LIE.

The primary endpoint was the clinical success rate in each treatment in the modified intention to treat (ITT) population (i.e. all randomised patients who received at least one dose of study drug). The definition of success included judgement of cure or improvement and a negative blood culture.

This was measured at the test of cure (TOC) visit 42 days after the end of therapy. The non-inferiority test for the primary endpoint used a lower bound of the confidence intervals (CI) of 20% for daptomycin minus comparator and the upper bound containing 0.

In the modified ITT population, overall success was reported in 44% (53/120) daptomycin and 42% (48/115) standard therapy patients; absolute difference of 2.4% (95% CI: -10% to 15%). In the per protocol (PP) population, overall success was reported in 54% (43/79) and 53% (32/60) patients in each group respectively; absolute difference 1.1% (95% CI: -16% to 18%). In patients infected with MSSA, the overall success rate was 45% (33/74) in daptomycin and 49% (34/70) in standard therapy patients; absolute difference -4.0% (95% CI: -20% to 12%) and with MRSA 44% (20/45) and 32% (14/44) patients respectively; absolute difference 13% (95% CI: -7.4% to 33%). Only 19 daptomycin-treated patients and 16 standard therapy patients of the modified ITT population had a final diagnosis (made by the adjudication committee) of uncomplicated or complicated RIE. The overall success rates in these patients were 42% (8/19) and 44% (7/16) respectively; absolute difference –1.6% (95% CI: -35% to 31%).

Failure rates at the TOC visit (clinical failure, microbiological failure, death, no blood culture, use of potentially effective non-study antibiotics, or premature discontinuation of study drug because of clinical or microbiological failure or adverse event) were 56% (67/120) in daptomycin and 58% (67/115) in standard therapy patients. However, the reasons for failure differed between the groups with numerically, but not significantly, more patients failing on microbiological grounds in the daptomycin group (16% (19/120) versus 9.6% (11/115); and numerically, but not significantly, more failures due to adverse events in the standard therapy group, 15% (17/115) versus 6.7% (8/120) patients.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

There was no significant difference between daptomycin and standard therapy in the overall incidence of adverse events. Elevated creatine kinase levels occurred more frequently in the daptomycin group (6.7% versus 0.9%). Renal impairment (defined as interstitial nephritis, toxic nephropathy, acute prerenal failure, acute or chronic renal failure, renal impairment or renal tubular necrosis) was reported in 18% of standard therapy and 6.7% of daptomycin patients. When defined on the basis of worsening creatinine clearance, the corresponding incidences were 47% and 20%.

Summary of clinical effectiveness issues

The open-label design of the study could have allowed bias as, despite the independent adjudication committee making the final diagnosis, assessing the outcomes, and being blinded to treatment allocation, investigators could still withdraw more patients from one treatment group than the other.

In studies testing non-inferiority, the primary analysis is usually performed in the PP population since this is most sensitive for detecting any real difference in efficacy between the groups.

However in this study, patients were excluded from the PP population for a number of reasons (treatment <4 days, <80% of dose, no evaluations at specified time points, non-evaluable by IEAC) and the PP population was therefore considerably smaller than the modified ITT population (59% (139/235), with 79 patients in the daptomycin group and 60 in the comparator group). However, within both the modified ITT and PP populations, the 95% CIs for the difference between groups fell within the predefined margins for non-inferiority.

While definite or possible infective endocarditis (IE) accounted for 75% (90/120) of the baseline diagnosis in the daptomycin group, this was only confirmed as a final diagnosis by the adjudication committee as RIE in 16% (19/120) patients. Similarly in the standard therapy group, 79% (91/115) patients had an initial diagnosis of definite or possible IE, but only 14% (16/115) were subsequently diagnosed with RIE. Of the confirmed RIE patients, 15/35 were infected with MRSA. Therefore, the number of study patients with MRSA RIE were very limited.

There does not appear to be a clear reason why there were more microbiological failures in the daptomycin than the standard therapy group (16% versus 9.6%). Notably, in 6 of these daptomycin-treated patients, *S.aureus* demonstrated increasing daptomycin minimum inhibitory concentrations (MICs).

Daptomycin offers a more convenient once-daily dosing regimen than vancomycin and does not require plasma levels to be monitored.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing daptomycin to vancomycin as first line therapy for patients with *S. aureus* bacteraemia caused by MRSA, with or without endocarditis. The main assumption was that using daptomycin would reduce treatment duration by 1.4 days, and this would save 1.4 days of hospitalisation for patients. The result was a saving of £32 per patient in the daptomycin arm (£16,503 compared to £16,535). No evidence was submitted for patients with MSSA bacteraemia.

Using a cost-minimisation analysis approach was acceptable given the clinical evidence demonstrated the equivalent efficacy of daptomycin and vancomycin. The main issues with the submission include:

- The assumed saving in treatment duration of 1.4 days is unlikely to occur in clinical practice.
- In the standard care arm, 71% of patients who discontinue vancomycin due to adverse events or failure are assumed to switch to daptomycin. This is not current practice and thus an inappropriate comparator.

However, despite these limitations, daptomycin offers a potentially useful additional treatment option with a benefit over some existing medicines in that it does not require therapeutic drug monitoring.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Guidelines from an advisory group of the British Cardiac Society and the Royal College of Physicians on the prophylaxis and treatment of infective endocarditis in adults were published in 2004. They recommend six weeks of antibiotic treatment for IE due to Staphylococcus on native valves.

For MSSA infection, the guideline recommends flucloxacillin (plus 3-5 days of gentamicin); for MRSA, vancomycin (plus 3-5 days of gentamicin) is recommended. It is noted that linezolid and quinupristin/dalfopristin may be used in MRSA. However, neither agent is licensed for this indication.

Guidelines from a joint working party comprising the British Society for Antimicrobial Chemotherapy, Hospital Infection Society and Infection Control Nurses Association on the prophylaxis and treatment of MRSA in the UK were published in 2006. They recommend a minimum duration of 14 days' treatment with glycopeptides or linezolid for uncomplicated bacteraemia and longer treatment in patients with, or at higher risk of, endocarditis, and echocardiographic assessment is important.

Additional information: previous SMC advice

After review of a full submission on 10th March 2006, SMC advised that 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

Additional information: comparators

Other antibacterials with activity against MRSA. Vancomycin and teicoplanin are the most likely comparators and are licensed for use in endocarditis and cSSTI. Other possible alternatives include linezolid and quinupristin/dalfopristin although they are not licensed for endocarditis.

Cost of relevant comparators

Drug	Dose regimen	Cost per course of 42 days (£)
Daptomycin	**6mg/kg daily by IV infusion**	**2604-3720***
Teicoplanin	400mg by IV injection or infusion every 12 hours for three doses then 400mg daily	1567
Vancomycin	1g twice daily by IV infusion	1091

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26.11.07.

* The costs for daptomycin are based on patients weighing <60kg (and receiving 350mg daily) to up to 80kg (and receiving up to 500mg daily).

Additional information: budget impact

The manufacturer estimated that the annual drug budget to manage patients with endocarditis and bacteraemia would be £ £5.83m in year 1 and £6.16m in year 5. Given the cost of existing treatments, this implied an increase of £4600 in year one and £335k in year five as a result of adopting daptomycin. The number of patients treated with daptomycin was assumed to be 15 in year 1 rising to 1,027 in year 5.

Healthcare savings of £32 per patient were assumed resulting in absolute savings in healthcare costs of £460 in year 1 rising to £33,162 in year 5. Many of these patients will have cSSTI and it is not appropriate to include them in the budget impact for this submission. The assumed savings of £32 per patient over each inpatient stay are not appropriate given the results from the study for this patient group.

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 10 January 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission.

Fowler VG, Boucher HW, Corey GR et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006; 355: 653-65.

European Medicines Agency (EMEA). European public assessment report (EPAR) for daptomycin. www.emea.eu.int