Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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dalbavancin 500mg powder for concentrate for solution for infusion (Xydalba®)

SMC No. (1105/15)

Allergan/Actavis

06 November 2015 *(Issued December 2016)*

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dalbavancin (Xydalba®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

SMC restriction:

- for second-line use or when meticillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected, or on the advice of local microbiologists or specialists in infectious disease, and
- the patient is initially hospitalised due to ABSSSI, requires intravenous antibiotics, but is eligible for early discharge as soon as their medical condition does not require further inpatient treatment.

In two phase III double-blind studies of patients with ABSSSI, dalbavancin was non-inferior to the comparator for clinical response at end of treatment in the clinically evaluable population.

Overleaf is the detailed advice on this product.

Vice-Chairman,
Scottish Medicines Consortium

Published 16 January 2017

Indication

Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Dosing Information

Dalbavancin 1,000mg followed, one week later, by dalbavancin 500mg. Dalbavancin is administered by intravenous (IV) infusion over a 30 minute period.

Product availability date

23 November 2016

Summary of evidence on comparative efficacy

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic, structurally related to teicoplanin. Dalbavancin interrupts cell wall synthesis, which results in bacterial cell death. It has activity against gram-positive bacteria including strains of meticillin-resistant *Staphylococcus aureus* (MRSA) and some *Staphylococcus aureus* with reduced susceptibility to glycopeptides. Its pharmacokinetic profile allows once-weekly intravenous (IV) dosing. The term acute bacterial skin and skin structure infections (ABSSSI) refers to cellulitis/erysipelas, wound infections and major cutaneous abscesses with a lesion area size of ≥75cm^2 (lower for areas that involve certain body surface sites, such as the face).[1,2]

The submitting company has requested that SMC considers dalbavancin when positioned for use in adults who are initially hospitalised due to ABSSSI, require intravenous antibiotics, but are eligible for early discharge as soon as their medical condition does not require further inpatient treatment.

Evidence for efficacy comes from two key phase III double-blind, non-inferiority studies (DISCOVER 1 and DISCOVER 2) conducted in patients with ABSSSI.[2-5] Patients aged 18 to 85 years were recruited if at least three days of IV therapy was considered to be required and patients had at least one systemic sign of infection within 24 hours before randomisation (body temperature >38^{o}C, white cell count >12,000 cells/mm^3 or >10% band forms on the white cell differential count). As well as erythema, patients were also required to have at least two local signs (purulent drainage or discharge, fluctuance, heat or localized warmth, tenderness on palpation, and swelling or induration).

Patients were randomised in a ratio of 1:1 to dalbavancin 1,000mg IV on day 1 and 500mg IV on day 8 or vancomycin 1,000mg (or 15mg/kg) IV every 12 hours for at least three days with an option to switch to linezolid 600mg orally every 12 hours to complete 10 to 14 days of treatment. Stratification was according to infection type and presence or absence of fever (so that the proportion of patients with a major abscess was ≤30% and with fever was ≥25%). Dalbavancin was given as an IV infusion over 30 minutes and vancomycin as an IV infusion over 120 minutes. The switch from vancomycin IV to oral linezolid could be done by the investigators if in the previous 24 hours, the patient had four temperature measurements ≤37.6°C and unequivocal improvement in some or all of the clinical signs of the SSSI under study. If some signs had not improved, then none should have worsened.[2,3]

The protocol-defined primary endpoint was early clinical response, defined as cessation of spread of erythema associated with infection and a temperature of ≤37.6^{o}C at three consecutive readings performed six hours apart. It was measured at 48 to 72 hours of therapy and determined after treatment was completed.[3]

The primary endpoint considered by the European Medicines Agency (EMA) was clinical status at the end of treatment in the clinically evaluable population. Clinical success occurred if the lesion area defined by erythema decreased from baseline, temperature was ≤37.6°C, there was no further need for systemic antibacterial treatment, fluctuance and localized heat/warmth were absent, and tenderness to palpation and swelling/induration were no worse than mild. For patients with a wound infection, the purulent drainage was to be improved and no worse than mild.[2] Analysis in the intention-to-treat (ITT) population was also considered important in order to robustly demonstrate non-inferiority.[6]

Results for the individual studies and pooled analysis are available. Non-inferiority was demonstrated based on the non-inferiority margin of -10% (lower limit of 95% CI) in the protocol defined and EMA preferred primary endpoint. Results are included in table 1.

Table 1: results of primary endpoints in DISCOVER 1 and DISCOVER 2 studies[2-5]

	DISCOVER 1		DISCOVER 2		Pooled analysis	
	dalbavancin	vancomycin-linezolid	dalbavancin	vancomycin-linezolid	dalbavancin	vancomycin-linezolid
	n=288	n=285	n=371	n=368	n=659	n=653
Early clinical response at 48 to 72 hours of treatment (ITT) (protocol-defined endpoint)						
% (n/N)	83% (240/288)	82% (233/285)	77% (285/371)	78% (288/368)	80% (525/659)	80% (521/653)
absolute difference (95% CI)	1.5% (-4.6% to 7.9%)		-1.5% (-7.4% to 4.6%)		-0.1% (-4.5% to 4.2%)	
Clinical status at end of treatment (clinically evaluable population/per protocol) (EMA)						
% (n/N)	87% (214/246)	91% (222/243)	94% (303/324)	93% (280/302)	91% (517/570)	92% (502/545)
absolute difference (95% CI)	-4.4% (-9.6% to 1.6%)		0.8% (-3.3% to 4.9%)		-1.5% (-4.8% to 1.9%)	
Clinical status at end of treatment (ITT) (EMA)						
% (n/N)	82% (236/288)	87% (247/285)	90% (332/371)	88% (322/368)	Not available	Not available
absolute difference (95% CI)	-4.8% (-10.5% to 1.2%).		2.0% (-2.4% to 6.8%)		Not available	

ITT = intention-to-treat; EMA = European Medicines Agency; CI = confidence interval; EMA=European Medicines Agency

Pre-planned sensitivity analyses of the primary endpoints supported the results of the protocol-defined and EMA primary endpoints.[3]

Investigator-assessed response at the end of therapy in the clinical per protocol population was a secondary endpoint. In pooled analysis the proportion of patients with successful investigator-assessed response was 96% (547/570) in the dalbavancin group and 97% (527/545) in the vancomycin-linezolid group, absolute difference -0.7% (95% CI: -3.0% to 1.5%). Pain resolved at similar rates between groups in both studies. Microbiological responses in patients with MRSA pathogen (microbiological evaluable population at end of treatment) were 89% versus 97% (DISCOVER 1) and 98% versus 100% (DISCOVER 2) in the dalbavancin and vancomycin-linezolid groups respectively.[2-5]

Additional efficacy data come from a double-blind, non-inferiority study (VER001-9) conducted in patients with complicated SSSI that were due to suspected or confirmed gram-positive pathogens that warranted IV treatment.[2,7,8] Patients were required to have at least two local signs and/or symptoms of

complicated SSSI (ie drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration) and at least one sign of systemic infection or of another complicating factor, indicating requirement for parenteral therapy.

Patients were randomised in a ratio of 2:1 to dalbavancin IV (doses as before) or linezolid 600mg IV every 12 hours with an option to switch to linezolid 600mg orally every 12 hours to complete 14 days of treatment. Criteria to switch from IV to oral were a decrease in fever or clinical improvement at the SSSI site after ≥24 hours of IV therapy.[7]

The primary end point was clinical success at the test of cure visit (12 to 16 days after completion of therapy) in the clinically evaluable population. A successful clinical response was defined as signs and symptoms of SSSI that had improved such that no further antibacterial therapy was warranted. The proportion of patients with clinical success was 89% (386/434) in the dalbavancin group and 91% (206/226) in the linezolid group; absolute difference -2.21% (95% CI: -7.28% to 2.86%). Non-inferiority was demonstrated based on the non-inferiority margin of -12.5% (lower limit of 97.5% CI). The proportion of patients with clinical success (ITT analysis) was 76% (437/571) in the dalbavancin group and 83% (234/283) in the linezolid group; absolute difference -6.15% (95% CI: -12.03% to -0.27%). However the ITT analysis considered patients classed as 'indeterminates' (those who received <72 hours of study medication or who did not present for evaluation) as failures. There was an imbalance between the groups with respect to indeterminates that biased against dalbavancin. In a post hoc analysis of clinical success at test of cure visit (ITT population, excluding 'indeterminates') the proportion of patients with clinical success was 90% (437/486) in the dalbavancin group and 92% (234/254) in the linezolid group; absolute difference -2.20% (95% CI: -6.7% to 2.3%).[2,7,8]

Microbiological response at test of cure visit included eradication or presumed eradication of all baseline gram-positive pathogens. In the microbiologically evaluable population the proportion of patients with a microbiological response was 90% in the dalbavancin group and 88% in the linezolid group and in patients with MRSA pathogen was 91% and 89% in the respective groups. Overall response rate (that included clinical and microbiological responses) at test of cure visit in the clinically evaluable population was 88% in the dalbavancin group and 87% in the linezolid group.[2,7]

Summary of evidence on comparative safety

In pooled analysis of DISCOVER 1 and DISCOVER 2 any adverse event occurred in 33% (214/652) of dalbavancin-treated patients and 38% (247/651) of vancomycin-linezolid-treated patients and treatment-related adverse events in 12% (80/652) and 14% (89/651) of patients respectively. Adverse events that led to premature discontinuation of study drug occurred in a similar proportion of patients in each group; 2.1% (14/652) and 2.0% (13/651) respectively.[3]

The most common adverse events in the dalbavancin and vancomycin-linezolid groups respectively were nausea (2.5% [16/652] versus 2.9% [19/651]), diarrhoea (0.8% [5/652] versus 2.5% [16/651]) and pruritus (0.6% [4/652] versus 2.3% [15/651]).

Within the dalbavancin and vancomycin-linezolid groups treatment-related, serious adverse events occurred in 0.3% (2/652) and 0.6% (4/651) of patients respectively; cellulitis and anaphylactoid reaction (in the dalbavancin group) and cellulitis, gastrointestinal disorder, toxic nephropathy and acute renal failure (in the vancomycin-linezolid group), all occurring in one patient each.

In the VER001-9 study, three serious adverse events were considered related to study treatment; one in the dalbavancin group (leukopenia which resolved spontaneously) and two in the linezolid group

(moderate thrombocytopenia which resolved spontaneously and severe pancytopenia which resolved with treatment).[7]

Summary of clinical effectiveness issues

Dalbavancin is licensed for the treatment of ABSSSI in adults. SMC has accepted ceftaroline, tigecycline, daptomycin and tedizolid in ABSSSI for restricted use on the advice of microbiologists or specialists in infectious diseases. The restrictions are mainly to use second-line or in MRSA infections.

The submitting company has requested that SMC considers dalbavancin when positioned for use in adults who are initially hospitalised due to ABSSSI, require intravenous antibiotics, but are eligible for early discharge as soon as their medical condition does not require further inpatient treatment. Clinical experts consulted by SMC reported that flucloxacillin IV is first-line treatment choice and vancomycin IV is used second-line, or when MRSA is present. If patients require IV treatment on discharge from hospital then ceftriaxone (when there is no evidence of MRSA), teicoplanin or daptomycin are prescribed. Clinical experts also noted use of linezolid (IV/oral) and tedizolid (oral). No comparative efficacy data versus IV flucloxacillin and IV ceftriaxone, were included in the company's submission. Therefore this positions dalbavancin as a second-line treatment option or in MRSA suspected infections. SMC agreed to further refine the restriction to take account of this additional positioning.

The non-inferiority of dalbavancin versus vancomycin-linezolid was demonstrated for the protocol-defined primary endpoint in the DISCOVER studies using the EMA accepted non-inferiority margin of -10%.[2] Treatment outcomes in both groups were similar when analysed according to infection type, underlying illness, and severity of infection. Around 25% of patients received their treatment as out-patients.[3] Non-inferiority was also demonstrated (using a non-inferiority margin of -12.5%) in the VER001-9 study.[7]

However EMA guidance notes that the ITT and per protocol analyses have equal importance in non-inferiority studies, indicating that to demonstrate non-inferiority both populations should be used.[6] Results in the ITT population for the EMA-designated primary endpoint in DISCOVER 1 indicate that non-inferiority was not demonstrated as the lower confidence interval was 0.5% outside the non-inferiority margin.[4]

During the design of the DISCOVER studies the Committee for Medicinal Products for Human Use (CHMP) advised that a high proportion of patients recruited to the study should meet at least two systemic inflammatory response syndrome (SIRS) criteria and patients should be considered to require seven days of IV therapy, to ensure the exclusion of patients with non-severe infections. However the inclusion criteria for both studies required that patients had at least one sign of systemic infection and required at least three days of IV therapy. Despite this, the EMA considered that a large proportion of patients included in the studies had severe infections (over 60% and 40% in the DISCOVER 1 and 2 studies, respectively, met the SIRS criteria).[2]

The patient populations of the studies may differ to those in which dalbavancin would be used in clinical practice. Although the DISCOVER studies were planned to be conducted in areas where the prevalence of MRSA was high, the proportion of MRSA isolates was around 21%, and compares with around 45% in the VER001-9 study. The proportion of patients with diabetes mellitus, in the pooled population of DISCOVER studies, was around 13% and in the VER001-9 study was 23%. Across the studies clinical response in the subgroup of patients with diabetes mellitus and microbiological response in subgroup of patients with MRSA infections were generally supportive of analyses in the complete study populations.[2,3,7]

The submitting company conducted a network meta-analysis (NMA) in order to indirectly compare dalbavancin with daptomycin, linezolid, teicoplanin, tigecycline and vancomycin. Fixed-effect and random-effect models were developed and results for the model with the best fit for each endpoint were reported. Two efficacy endpoints (clinical success and microbiological success) and four safety endpoints were analysed. A total of 20 studies were included in the NMA. In order to incorporate teicoplanin in the network three studies with mixed children and adult populations (one of which had a teicoplanin arm) were included. Results of the NMA favoured vancomycin in terms of efficacy, although linezolid has the highest probability of being the best treatment for efficacy outcomes. For adverse event rate, serious adverse event rate and all cause mortality dalbavancin was favoured over some comparators. However the results of the NMA are limited by heterogeneity in study design and baseline characteristics (including proportion of patients with diabetes mellitus, peripheral vascular disease and MRSA infection) and differing results of outcomes in common control arms. Overall, the conclusion of no evidence of real differences between dalbavancin and comparators seems reasonable, although there are considerable limitations with the NMA. The results of the NMA are relevant to the economic scenario analysis.

Dalbavancin is administered as a 30 minute IV infusion on days 1 and 8 and is likely to have advantages over other parenteral antibiotics which are administered more frequently, and some of which require therapeutic drug monitoring. Clinical experts consulted by SMC considered that dalbavancin is a therapeutic advancement in terms of its weekly administration schedule. They considered the treatments likely to be displaced by dalbavancin are IV teicoplanin, ceftriaxone and daptomycin (given in out-patient setting). However patients may be switched to oral antibiotics when clinically indicated and in this situation use of linezolid has been reported. Advantages versus oral antibiotics are potentially in relation to treatment compliance.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis which compared dalbavancin against vancomycin and linezolid in adult patients with ABSSSIs who are hospitalised for their infection, require IV antibiotic treatment, and are potentially eligible for early discharge in Scotland. As noted above, given the comparators selected, this positions dalbavancin as a second-line treatment option or in MRSA suspected infections.

The company used a decision analytic model to assess the cost-effectiveness of dalbavancin versus the comparators. The time horizon used in the analysis was two months.

In terms of model structure patients enter the model at initiation of therapy and can remain on treatment in hospital for the full duration of therapy (14 days). Some patients may be discharged early from hospital after 3 days and complete treatment through outpatient parenteral antibiotic therapy (OPAT). After 3 days patients could also switch to an alternative IV treatment due to a lack of efficacy and remain hospitalised for the full duration of therapy (17 days). Mortality was included in the model as patients could die from other causes after 3 days. The analysis also took into account disease recurrence which applied to 5% of patients in the dalbavancin and comparators arms. Patients who experienced recurrence were hospitalised for the duration of therapy (14 days).

The main sources of clinical data used in the analysis were the DISCOVER 1, DISCOVER 2 and VER001-9 studies which provided evidence of the non-inferiority of dalbavancin versus the comparators in the analysis. These data also provided estimates of the proportion of patients who switched to alternative treatments for all arms of the analysis, mortality, and the proportion of patients treated with dalbavancin who would be eligible for early discharge (89.9%). The proportion of patients eligible for

early discharge in the comparator arm of the analysis (69.2%) was informed by data from a Scottish study based in Glasgow hospitals.

Medicines costs were included in the analysis as were costs associated with hospitalisation, OPAT costs, healthcare professional visit costs, and tests and procedures.

The cost-minimisation analysis reported that the cost per patient treated with dalbavancin was £5,073. The cost of vancomycin and linezolid was £7,453 and £8,241 respectively. On the basis of these findings, dalbavancin would be the cost-effective treatment option.

The company provided a scenario analysis which included daptomycin and teicoplanin as comparators. The estimated cost of daptomycin and teicoplanin were £6,850 and £6,180 respectively while the cost of dalbavancin, vancomycin and linezolid remained the same as the base case analysis. Therefore dalbavancin was also the cost-effective option in this scenario.

The company provided a number of additional scenario analysis and in most cases dalbavancin was less expensive than the comparators. However when patients treated with vancomycin and linezolid were switched to oral linezolid upon early hospital discharge, the cost of vancomycin and linezolid reduced to £4,559 and £4,767 respectively. Therefore in this scenario the cost-effective option was vancomycin and not dalbavancin.

The main weaknesses were:

- In the economic model all patients initially received treatment as an inpatient and a proportion of patients may complete treatment through OPAT. However some patients were not discharged to outpatient services and therefore completed their treatment in hospital. As a result the economic model considers patients in an inpatient and outpatient setting and a number of comparators may be relevant which introduced some uncertainties. SMC clinical experts suggested that IV vancomycin and IV linezolid would not be used as outpatient treatments as they require twice daily dosing. One SMC expert suggested that IV vancomycin followed by IV teicoplanin could be considered standard treatment. The company did provide a sensitivity analysis where patients initiated to vancomycin and linezolid received teicoplanin upon early hospital discharge and there were no differences in rate of early hospital discharge. In this scenario dalbavancin cost £5,073 per patient while vancomycin and linezolid reduced to £5,693 and £5,901 respectively. Further in relation to comparators, the company did not provide any economic analysis compared to IV flucloxacillin and IV ceftriaxone, and as noted above, this therefore this suggests use of dalbavancin as a second-line treatment option or in MRSA suspected infections.
- The base case analysis assumed that patients who continue treatment with vancomycin or linezolid remain on IV treatment for the duration of therapy (14 days). The company has provided a scenario analysis where patients initiated to vancomycin and linezolid could switch to oral linezolid if discharged early. This analysis reported dalbavancin was no longer the cost-minimising option however SMC expert responses have indicated that oral linezolid may not be used frequently in this group of patients. It is also worth noting that in the pivotal studies patients initiated to vancomycin or linezolid could switch to oral linezolid and the company has reported that a large proportion of patients switched treatments. Therefore the pivotal study data may be more representative of patients switching to oral linezolid than the treatment sequences modelled in the base case.
- The analysis assumed that 89.9% of patients treated with dalbavancin would be eligible for early discharge. This figure is based on the proportion of patients who switched to oral placebo from the pivotal studies. The SMC expert responses regarding this assumption were mixed. One expert suggested that this figure was reasonable and reflected clinical practice, however other experts have commented that there is limited information to comment. The company has

provided a scenario analysis where 70% of dalbavancin patients were discharged early and dalbavancin remained the cost-minimising treatment option.

- The economic model assumed that patients eligible for early discharge would be discharged after 3 days. Therefore in the dalbavancin arm of the analysis a large proportion of patients (89.9%) would be discharged only a few days after being admitted to hospital. The SMC expert responses regarding this assumption were again mixed. Some experts commented that the assumption was plausible while another expert also suggested this was unlikely. However, the company provided an analysis where patients potentially eligible for early discharge were discharged on day 8 and dalbavancin remained cost-minimising versus the comparators.

Despite these uncertainties the economic case has been demonstrated in second-line use or when meticillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected or on the advice of local microbiologists or specialists in infectious disease in adult patients who are hospitalised for their infection, require IV antibiotic treatment, and are potentially eligible for early discharge in Scotland.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from the Skin Conditions Campaign Scotland (SCCS), which is a registered charity.

- SCCS has received pharmaceutical company funding in the past two years, but not from the submitting company.

- The main ABSSSIs are conditions such as impetigo, erysipelas, cellulitis, wound infections and abscesses. Patients in hospital, care homes and at home with low immune systems and the elderly are particularly susceptible. Acute infections are disabling in the short term, causing fever, pain and tenderness. More serious infections can spread and be life-threatening. Particularly worrying, and difficult to live with, is the information that you carry an antibiotic resistant bacterium for which treatment is limited, that you are a risk to other people, and may have to be isolated from other people.

- Effective treatment of ABSSSIs improves the quality of life for patients and those who live and work with them and care for them. New antibiotics, effective against resistant organisms, are important and essential treatments in the fight against MRSA.

- It is necessary to use these antibiotics in a restricted way, as part of a strategy of improved diagnosis, rapid effective treatment regimes that reduce risk of antimicrobial resistance, treats diseased skin and reduces the risk of recurrent infection, and of spread to others. SCCS supports the introduction of dalbavancin as part of such a strategy.

Additional information: guidelines and protocols

The Scottish Antimicrobial Prescribing Group (SAPG), in conjunction with the Scottish Microbiology and Virology Network, published a best practice algorithm for the management of patients with *Staphylococcus aureus bacteriaemia* (SAB) in 2015. The algorithm indicates that empirical antibiotic therapy should be initiated promptly in all patients presenting with confirmed or suspected SAB. If MRSA is suspected this should consist of treatment with vancomycin in accordance with local protocols. In patients who are intolerant, allergic or not responding well to vancomycin, alternative treatment options should be discussed with an infectious disease specialist or microbiologist.[9]

The 2008 British Society for Antimicrobial Chemotherapy (BSAC) evidence based guideline for the management of MRSA infections in the UK includes a number of recommendations for management of skin and soft tissue infections (table 1). The guideline states that no recommendations could be made regarding new licensed agents due to a lack of real world data.[10]

Table 1: BSAC 2008 guideline recommendations for MRSA skin and soft tissue infections

Indication	Suggested treatment (dependent on susceptibility testing)
Impetigo and boils	• Topical mupirocin or fusidic acid
Cellulitis/surgical site infections; non-hospitalised	• Doxycycline or clindamycin unless the infection is severe or there is a high risk of bacteraemia or endocarditis • If MRSA strain is resistant then glycopeptides or linezolid should be used. Co-trimoxazole may also be considered. • Glycopeptides or daptomycin parental therapy may be considered cost effective for outpatient treatment where IV treatment is necessary
Cellulitis/surgical site infections; hospitalised	• Glycopeptides, linezolid or daptomycin for severe infection or where there is a high risk of bacteraemia • Tigecycline monotherapy may be considered in polymicrobial infections • *There is insufficient evidence to make a recommendation on treatment options after failure of glycopeptide monotherapy.*
Intravenous infusion sites	• Glycopeptide or linezolid • Mild infection may respond to oral agents

The BSAC guidance on the treatment of MRSA infections presenting in the community was also published in 2008.[11] A number of empirical antibiotic regimens are suggested for MRSA skin and soft tissue infections:

- Rifampicin (300mg orally twice daily) PLUS sodium fusidate (500mg three times a day) OR doxycycline (100mg orally twice daily) for five to seven days.
- Rifampicin (300mg orally twice daily) PLUS trimethoprim (200mg orally twice daily) for five to seven days.
- Linezolid (600mg orally twice daily) following discussion with Consultant Microbiologist or Infectious Disease physician.

Additional information: comparators

Vancomycin IV for first-line treatment of MRSA, then linezolid or teicoplanin; other treatments include ceftaroline fosamil, daptomycin, tigecycline and tedizolid.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
dalbavancin	**1,000mg by IV infusion on day 1, then 500mg IV on day 8**	**1,676**
linezolid	600mg orally or by IV infusion every 12 hours for 10 to 14 days	890 to 1,246
daptomycin	4mg/kg to 6mg/kg by IV infusion once daily	434 to 1,240
ceftaroline fosamil	600mg by IV infusion every 12 hours	525 to 1,050
tigecycline	Initial dose of 100mg by IV infusion followed by 50mg by IV infusion every 12 hours	485 to 937
tedizolid phosphate	200mg orally or by IV infusion once daily for six days	862
vancomycin	500mg by IV infusion every six hours or 1g by IV infusion every 12 hours	203 to 406
teicoplanin	400mg by IV injection/infusion or by intramuscular injection every 12 hours for three doses followed by 6mg/kg by IV injection/infusion or intramuscular injection once daily	59 to 110

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and Monthly Index of Medical Specialties on 31 August 2015 except for dalbavancin where cost is from Department of Health. Costs are based on 7 to 14 days treatment duration unless specified otherwise. Dose per weight calculations are based on a body weight of 70kg.

Additional information: budget impact

The estimated number of patients eligible for treatment was 14 in year 1 rising to 460 in year 5. Treatment uptake was estimated at 100% in year 1 and year 5 respectively.

The company estimated that the gross medicines budget impact in year 1 was £23k rising to £771k in year 5. As medicines were assumed to be displaced the net medicines budget impact was assumed to be £15k in year 1 rising to £492k in year 5.

The budget impact model estimated non-cash releasing savings due to hospitalisation, use of OPAT, HCP visits and tests and procedures. The net total budget impact was savings of £34k in year 1 rising to £1.1m in year 5.

References

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

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4. DUR001-301 CSR. A phase 3, randomized, double-blind, Double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections

5. DUR001-302 CSR. A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections.

6. European Medicines Agency. Points to consider when switching from superiority to non-inferiority. CPMP/EWP/482/99. 27 July 2000. http://www.ema.europa.eu/ema/

7. Jauregui L.E, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis. 2005;41:1407–15

8. VER001-9 CSR. Phase 3, randomized, double-blind, multi-center dtudy to evaluate the safety and efficacy of dalbavancin versus linezolid in the treatment of complicated skin and soft tissue infections with suspected or confirmed gram-positive bacterial pathogens

9. Scottish Antimicrobial Prescribing Group (SAPG) and Scottish Microbiology and Virology Network. *Staphylococcus aureus* bacteraemia management algorithm. 2015.

10. Gould F.K, Brindle R, Chadwick P.R. et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. J. Antimicrob. Chemother. 2009; 63 (5): 849-861.

11. Nathwani D, Morgan M, Masterton R.G. et al. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. J. Antimicrob. Chemother. 2008; 61 (5): 976-994.

This assessment is based on data submitted by the applicant company up to and including 8 December, 2016.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice

Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.