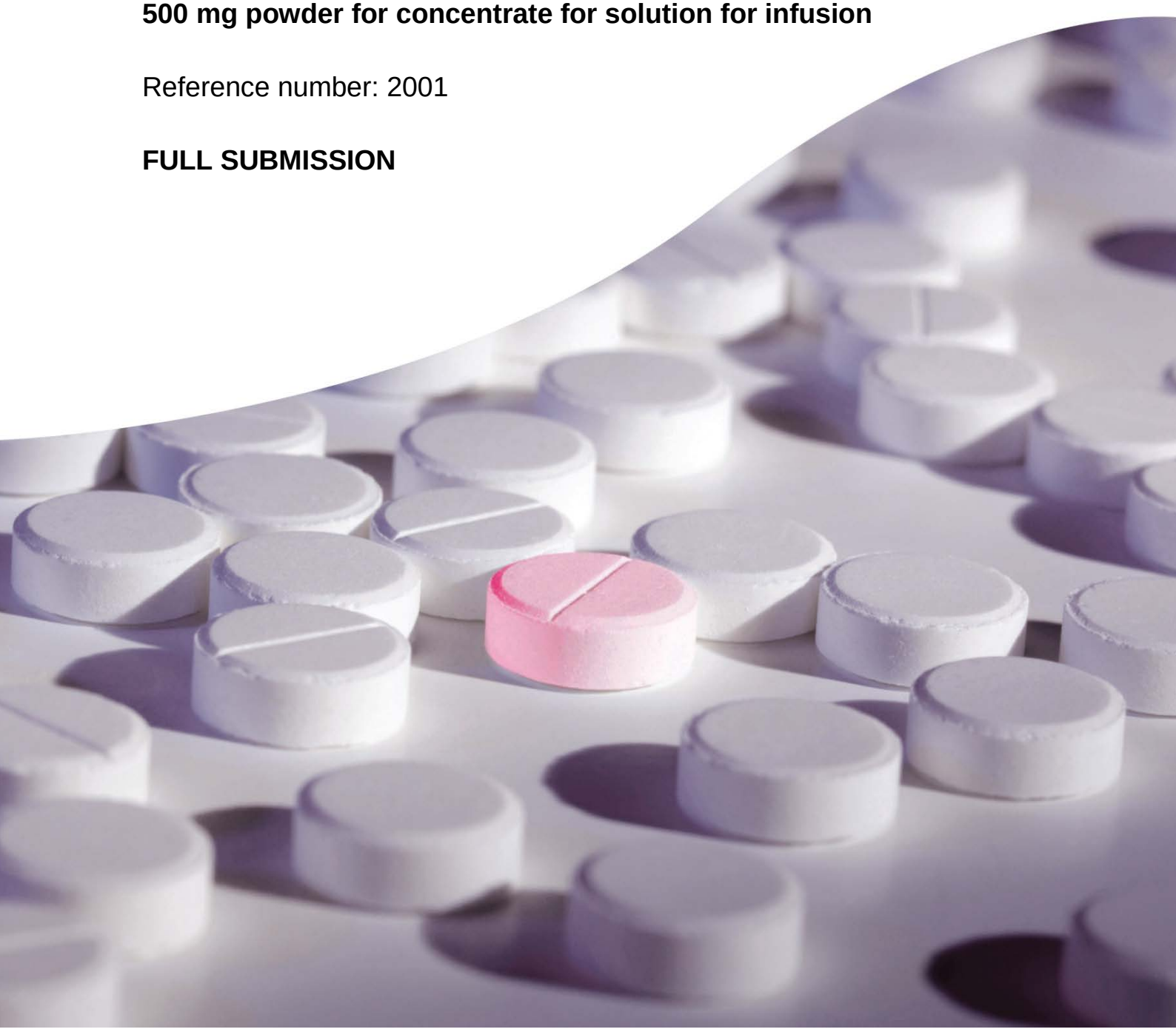
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Dalbavancin (Xydalba®)
500 mg powder for concentrate for solution for infusion

Reference number: 2001

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Dalbavancin (Xydalba®▼) 500 mg powder for concentrate for solution for infusion

1.0 KEY FACTS

Assessment details	Dalbavancin (Xydalba®▼) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. The company's submission focuses on the use of dalbavancin for second-line treatment or when methicillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected, or on the advice of local microbiologists or infectious disease specialists, and the patient is initially hospitalised due to ABSSSI and needs intravenous antibiotics but is eligible for early discharge. Dalbavancin's long half-life allows for 14 days of treatment to be delivered in a single dose or two once-weekly doses. Consideration should be given to official guidance on the appropriate use of antibacterial agents. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Current clinical practice	Current clinical practice in Wales is to treat ABSSSI with a range of oral and intravenous antibiotics depending on the type and severity of infection. If intravenous therapy is needed, flucloxacillin would usually be used first-line for non-MRSA infections and either vancomycin or teicoplanin used second-line or where MRSA was suspected. Other intravenous antibiotics would only be used on the advice of a microbiologist. The options for switching for patients eligible for early discharge would usually be ceftriaxone for non-MRSA infections or teicoplanin for MRSA infections.
Clinical effectiveness	Two phase III studies showed that dalbavancin was non-inferior to treatment with intravenous vancomycin switched to oral linezolid for treating ABSSSI. Both studies enrolled low numbers of patients with MRSA infection (< 30%), and excluded patients who had been given antibiotics for Gram positive bacterial infections in the 14 days before starting the study treatments. A network meta-analysis supported the comparability of dalbavancin to vancomycin and linezolid, and also associated dalbavancin treatment with fewer adverse events and lower all-cause mortality. However, the analysis is subject to a number of uncertainties.
Cost-effectiveness	A cost minimisation analysis assumed dalbavancin is equivalent to each of the comparators in respect to clinical outcomes. The base case analysis found that dalbavancin was cost saving

	compared to vancomycin and linezolid. The total cost per patient for a treatment of ABSSSI was £5,168 with dalbavancin. The comparative treatment cost when using vancomycin was £7,331 and for linezolid it was £8,119. The key cost drivers were lower relative outpatient parenteral antibiotic therapy (OPAT) and a reduction in hospital stay costs. Most scenario analyses reported dalbavancin as cost saving compared with the two comparators.
Budget impact	The estimated number of patients treated in Wales in Year 1 is 17. The company assumes an increase in patient numbers each year resulting in an estimated 178 patients in Year 5. The budget impact model shows net medicine acquisition costs of £18,394 in Year 1, rising to £190,525 in Year 5.

This assessment report is based on evidence submitted by Cardiome UK Ltd and an evidence search conducted by AWTTC on 23 March 2018[1].

2.0 BACKGROUND

2.1 Condition and clinical practice

Acute bacterial skin and skin structure infections (ABSSSI) are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*[2]. The incidence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing[2]. Because antibiotic resistance continues to emerge among Gram positive bacteria worldwide, there is an increasing medical need for new antibacterial agents with enhanced activity against these bacteria[2].

The US Food & Drug Administration defines ABSSSI as 'bacterial infections of the skin with a lesion size of at least 75 cm^2 (measured by an area of redness, oedema or induration) and includes: cellulitis; wound infection; and abscesses with surrounding cellulitis'[3].

There are no pan-European guidelines on managing ABSSSI[4], and no national guidelines in Wales. Local health board antimicrobial guidelines in Wales include a number of oral and intravenous antibiotics for treating ABSSSI in adults; the choice of regimen depends on the type and severity of the infection[5-10]. The intravenous agent most commonly included for first-line use is flucloxacillin and the antibiotics most commonly included for use where MRSA infection is suspected are vancomycin and teicoplanin[5-9].

AWTTC-sought opinion from clinical experts in Wales confirmed that where intravenous agents are needed, flucloxacillin would usually be considered first-line and vancomycin or teicoplanin are usually used second-line or where MRSA infection is suspected. Intravenous linezolid is rarely used in Wales. Oral linezolid treatment may sometimes be considered as a step-down from intravenous therapy, but patients eligible for early discharge would more likely be switched to intravenous ceftriaxone if there was no MRSA infection, or to intravenous teicoplanin if there was MRSA infection. Experts expected that dalbavancin would only be used in a small number of patients and only on a microbiologist's recommendation, rather than in empiric therapy.

2.2 Medicine

Dalbavancin is a lipoglycopeptide antibiotic that targets cell wall synthesis in Gram positive bacteria[11]. It was granted marketing authorisation in February 2015 for the treatment of ABSSSI in adults[11].

Dalbavancin has a long half-life (5–7 days) which is consistent with once-weekly dosing[11]. The recommended dose in adults is 1,500 mg given as either a single intravenous infusion of 1,500 mg, or an infusion of 1,000 mg followed by 500 mg one week later[11].

Within the licensed indication, the company anticipates that dalbavancin will be used in:

- second-line treatment of ABSSSI; or
- when MRSA infection is suspected; or
- on the advice of local microbiologists or infectious disease specialists; and
- the patient is at first hospitalised due to ABSSSI and needs intravenous antibiotics but is allowed early discharge as they don't need further inpatient treatment.

In this population, the company expects dalbavancin to displace vancomycin and linezolid.

2.3 Comparators

In its submission, the company listed these comparators:

- ceftriaxone;
- daptomycin;
- flucloxacillin;
- linezolid;
- teicoplanin; and
- vancomycin[1].

However, the comparators included in the company's economic evaluation are: linezolid and vancomycin, with scenario analyses for daptomycin and teicoplanin[1].

2.4 Guidance and related advice

- Welsh Analytical Prescribing Support Unit (2018) National prescribing indicators 2018–2019. Supporting information for prescribers[12]
- Welsh Analytical Prescribing Support Unit (2018) National prescribing indicators 2017–2018. Analysis of antibacterial prescribing data to December 2017[13]
- All Wales Medicines Strategy Group (2017) Primary care antimicrobial guidelines[14]
- Public Health Wales (2017) Antimicrobial resistance in Wales 2007–2016[15]
- Welsh Government (2016) Together for health. Tackling antimicrobial resistance and improving antibiotic prescribing[16]
- National Institute for Health and Care Excellence (2015) NICE guideline NG15. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use[17]
- National Institute for Health and Care Excellence (2014) NICE quality standard QS61. Infection prevention and control[18]
- Welsh Government (2014) Code of practice for the prevention and control of healthcare-associated infections[19]
- National Institute for Health and Care Excellence (2012) Clinical guideline CG139. Healthcare-associated infections: prevention and control in primary and community care[20]
- National Institute for Health and Care Excellence (2011) Public health guideline PH36. Healthcare-associated infections: prevention and control[21]

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of tedizolid phosphate (Sivextro®) and ceftaroline fosamil (Zinforo®)[22,23].

The use of oritavancin (Orbactiv®) to treat ABSSSI in Wales is not endorsed by AWMSG because no submission has been received from the marketing authorisation holder[24].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, dalbavancin (Xydalba®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes results from two randomised, double-blind phase III studies: DISCOVER 1 and 2. These compare dalbavancin given once weekly with vancomycin given twice daily followed by oral linezolid to treat acute bacterial skin and skin structure infections (ABSSSI). A third study provides supportive evidence: VER001-9 compared once-weekly dalbavancin with twice-daily linezolid to treat complicated skin and skin structure infections. These three studies and a network meta-analysis are used in the company's economic evaluation; all are discussed further in this section. A phase III study (DUR001-303) was included in the submission but will not be discussed further; it compared two different dosing regimens of dalbavancin: a single infusion of 1,500 mg versus two separate infusions of 1,000 mg and 500 mg given one week apart.

3.1 DISCOVER 1 and 2 studies

These studies were identically designed and aimed to compare the efficacy of dalbavancin treatment with vancomycin and linezolid treatment of ABSSSI in adults[25].

Patients were eligible to enrol if they were thought to need at least three days of intravenous therapy and had one or more systemic signs of infection before randomisation[25]. ABSSSI was diagnosed by the presence of cellulitis, a major abscess or a wound infection, each associated with at least 75 cm^2 of erythema; and at least two of these signs: purulent drainage or discharge, fluctuance, heat or localised warmth, tenderness on palpation and swelling or induration. Patients were excluded if they had received antibiotic treatment within 14 days before randomisation[25].

Patients were randomised to receive either dalbavancin or vancomycin with linezolid. Dalbavancin was given as a 1,000 mg dose intravenously over 30 minutes on Day 1, followed by 500 mg intravenously over 30 minutes on Day 8[25]. Vancomycin was given as a 1,000 mg dose (or 15 mg per kg body weight) intravenously over 120 minutes every 12 hours for at least three days, with an option to switch to oral linezolid at a dose of 600 mg every 12 hours, to complete 10 to 14 days of treatment. Patients in the dalbavancin group had a placebo infusion every 12 hours, and an oral placebo if there was a switch to oral therapy[25]. Patients could be switched to oral therapy if they had had four temperature measurements (taken 6 hours apart) that were ≤ 37.6°C in the previous 24 hours and there was unequivocal improvement in some or all of the clinical signs of the ABSSSI[26]. Both groups continued treatment for 10–14 days[25].

The primary endpoint was early clinical response, measured at 48–72 hours of therapy in the intention-to-treat population[25]. Treatment success was defined by two criteria: stopping the spread of the erythema associated with the infection; and a temperature of 37.6°C or lower at three consecutive readings taken six hours apart[25]. For marketing

authorisation, the European Medicines Agency also considered the endpoints of clinical status (success [decrease in erythema, temperature, tenderness, swelling/induration and purulent drainage] or failure) at the end of treatment in the clinically evaluable population and in the intention-to-treat population[2]. The non-inferiority margin chosen was 10 percentage points for the primary efficacy outcome[25].

Across both studies, 1,312 patients (aged 18–85 years) were randomised[25]. MRSA was present in < 30% of the pathogens isolated at baseline in the microbiological intention-to-treat population, in both studies[2]. In the dalbavancin groups, 608 of 659 patients completed the study treatment, and in the vancomycin with linezolid groups, 601 of 653 patients completed the study treatment[25].

In the intention-to-treat population of the DISCOVER 1 study, 75.1% of patients treated with vancomycin and linezolid and 72.2% of patients treated with dalbavancin switched to oral placebo treatment. In the intention-to-treat population of the DISCOVER 2 study, 90.2% of patients treated with vancomycin and linezolid and 91.1% of patients treated with dalbavancin switched to oral treatment. Similar results were seen for the clinically evaluable at the end-of-treatment population. The results are presented in Table 1. Once-weekly dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid to treat ABSSSI[25].

Table 1. Primary endpoint data for the DISCOVER 1 and 2 studies[2,25-27]

Endpoint	Dalbavancin % (n/N)	Vancomycin with linezolid % (n/N)	Absolute difference (95% CI)
Success rate at 48–72 hours after starting treatment in the intention-to-treat population*			
DISCOVER 1	83.3 (240/288)	81.8 (233/285)	1.5 (−4.6 to 7.9)
DISCOVER 2	76.8 (285/371)	78.3 (288/368)	−1.5 (−7.4 to 4.6)
Both studies	79.7 (525/659)	79.8 (521/653)	−0.1 (−4.5 to 4.2)
Clinical status at the end of treatment in the clinically evaluable per-protocol population†			
DISCOVER 1	87.0 (214/246)	91.4 (222/243)	−4.4 (−9.6 to 1.6)
DISCOVER 2	93.5 (303/324)	92.7 (280/302)	0.8 (−3.3 to 4.9)
Both studies	90.7 (517/570)	92.1 (502/545)	−1.5 (−4.8 to 1.9)
Clinical status at the end of treatment in the intention-to-treat population†			
DISCOVER 1	81.9 (236/288)	86.7 (247/285)	−4.8 (−10.5 to 1.2)
DISCOVER 2	88.7 (329/371)	85.6 (315/368)	3.1 (−1.8 to 8.0)

* Protocol primary endpoint
† Endpoint considered by the European Medicines Agency
CI: confidence interval; n: number of patients; N: total number of patients

Dalbavancin treatment was associated with a successful clinical outcome in 89.2% of patients with MRSA infection[25]. Other secondary outcomes generally supported the primary endpoint results and subgroup analyses showed no differences in clinical outcome.

3.2 Study VER001-9

This study compared the efficacy and safety of dalbavancin treatment with linezolid treatment of complicated skin and skin structure infections (SSSI) in adults[28].

Patients were enrolled in the study if they had a complicated SSSI that needed parenteral therapy[28]. A complicated SSSI was defined as an infection involving deeper soft tissue or that needed surgical intervention, or if MRSA infection was known or suspected. Patients also had to have at least two other local signs of complicated SSSI (drainage or discharge, erythema, fluctuance, heat or localised warmth, pain or tenderness on palpation, or swelling or induration) and at least one sign of a systemic infection or other complicating factor that needed parenteral therapy. MRSA was identified in 51% of patients[28].

Patients were randomised in a 2:1 ratio to receive either dalbavancin or linezolid for 14 days of treatment[28]. Dalbavancin was given as an intravenous infusion of 1,000 mg on Day 1, followed by 500 mg on Day 8, with a possible switch to oral placebo. Patients in this group received a placebo infusion every 12 hours until the treatment was switched to oral placebo. Linezolid was given intravenously in a 600 mg dose every 12 hours, with an option to switch to an oral 600 mg dose[28]. After at least 24 hours of intravenous therapy patients could switch to oral therapy if they had a sustained decrease in temperature for at least 12 hours or if there was improvement in the clinical signs of infection at the SSSI site[29].

The primary endpoint was clinical response at the test-of-cure visit, 14 ± 2 days after completing treatment (Day 28) in the clinically evaluable population[28]. A successful clinical response was defined as improvement in signs and symptoms of infection so that antibiotic therapy was no longer needed[28]. The European Medicines Agency considered this endpoint in the clinically evaluable population and in the intention-to-treat population[2]. A non-inferiority margin of 12.5% was used in the statistical analysis[28].

In the intention-to-treat population, 89.1% of patients treated with dalbavancin and 93.6% of those treated with linezolid switched to oral treatment[29]. Table 2 shows the primary endpoint results. Two doses of dalbavancin (1,000 mg given on Day 1 followed by 500 mg on Day 8) were non-inferior to linezolid given twice daily for 14 days[28]. Microbiological success was similar between treatment groups at the end-of-treatment and test-of-cure visits. For MRSA the eradication rates at the test-of-cure visit were 91% for the dalbavancin group and 89% for the linezolid group[28].

Table 2. Primary endpoints in study VER001-9[2]

Endpoint: clinical response at the test-of-cure visit	Dalbavancin % (n/N)	Linezolid % (n/N)	Difference (95% CI)
Clinically evaluable population*	88.9 (386/434)	91.2 (206/226)	−2.2 (−7.3 to 2.7)
Intention-to-treat population†	76.5 (437/571)	82.7 (234/283)	−6.2 (−12.0 to −0.3)

* Protocol primary endpoint
† Endpoint considered by the European Medicines Agency
CI: confidence interval; n: number of patients; N: total number of patients

3.3 Network meta-analysis

A systematic literature review was conducted in 2015 to compare the efficacy and safety of dalbavancin with other antibiotics used to treat ABSSSI in adults[30]. A total of 17 randomised, controlled trials met the inclusion criteria for a network meta-analysis[30].

Treatments in these studies included: vancomycin (16 studies), linezolid (6), daptomycin (5), tigecycline (4) and dalbavancin (3)[4].

The network meta-analysis used Bayesian principles and both fixed-effects and random-effects models[30]. All analyses were restricted to the intention-to-treat population; defined as all randomised patients in each group[30].

The results showed no statistically significant differences between dalbavancin and any of the comparator antibiotics for clinical treatment success or microbiological success[4]. The results comparing dalbavancin with vancomycin and linezolid are shown in Table 3.

Table 3. Network meta-analysis: efficacy and safety-related endpoints for the adult subgroups[4]

Endpoint	Odds ratio (credible interval)	
	Dalbavancin versus vancomycin	Dalbavancin versus linezolid
Clinical treatment success*	0.99 (0.68 to 1.51)	0.69 (0.41 to 1.00)
Microbiological success*	1.31 (0.40 to 4.93)	0.53 (0.11 to 1.85)
Discontinuation due to adverse events/serious adverse events†	1.08 (0.59 to 1.98)	1.24 (0.68 to 2.30)
Patients experiencing adverse events†	0.85 (0.70 to 1.03)	0.78§ (0.62 to 0.98)
Patients experiencing severe adverse events†	0.54§ (0.30 to 0.96)	0.99 (0.61 to 1.66)
All-cause mortality†	0.26§ (0.05 to 0.93)	0.20§ (0.04 to 0.77)

* using a random effects model
† using a fixed effects model
§ statistically significant

To include teicoplanin in the network meta-analysis, the selection criteria were broadened. Three additional studies were identified in mixed populations of adults and children, including one comparing teicoplanin with linezolid[4]. For clinical treatment success, the odds ratio for dalbavancin versus teicoplanin was 1.67 (credible interval 0.44 to 7.37). The clinical treatment success and microbiological success results for dalbavancin versus vancomycin and linezolid from the 20-study network were similar to those seen for the analysis of 17 studies[4].

3.4 Comparative safety

Overall, there are no new safety concerns. The adverse event profile for dalbavancin is as expected for a glycopeptide antibiotic[2]. However, when used at the dosing regimen recommended in the marketing authorisation, dalbavancin has not been clearly associated with the nephrotoxicity and ototoxicity seen with vancomycin and teicoplanin[2]. The most common adverse events reported with dalbavancin treatment are: nausea, headache, diarrhoea, constipation and vomiting; mostly of mild-to-moderate intensity[2].

In the DISCOVER studies, adverse events were reported in fewer patients treated with dalbavancin than in those who received vancomycin and linezolid; most were mild and considered unrelated to the study treatment[25]. The incidence of serious treatment-related adverse events was similar between groups (dalbavancin: 0.3% versus vancomycin and linezolid: 0.6%) as was the incidence of death (0.2% versus

1.1%) and adverse events leading to discontinuation of treatment (2.1% versus 2.0%)[25]. In study VER001-9, a higher proportion of patients in the linezolid group (32.2%) reported adverse events judged possibly related to treatment compared with those treated with dalbavancin (25.4%)[28]. In the dalbavancin group 3.9% of patients discontinued treatment because of adverse events, as did 3.2% of patients in the linezolid group. Serious adverse events were reported by 8% of patients overall (7.5% treated with dalbavancin and 8.5% treated with linezolid), though most were considered to be unrelated or unlikely related to the study treatment[28].

Similar results were shown in a pooled analysis of seven clinical studies in 3,002 patients with skin and skin structure infections treated with dalbavancin (n = 1,778) or a comparator antibiotic (n = 1,224)[31].

3.5 AWTTC critique

- Dalbavancin is a new lipoglycopeptide antibiotic, licensed to treat ABSSSI. The company expects dalbavancin to be used as second-line treatment, or for suspected MRSA infection, or on the advice of local microbiologists or specialists in infectious disease for people who are hospitalised with ABSSSI and need intravenous antibiotics but are eligible for early discharge[1].
- The clinical evidence presented compares dalbavancin with vancomycin and linezolid. However, AWTTC-sought clinical expert opinion suggests that vancomycin, teicoplanin and ceftriaxone would be the most appropriate comparators when considering the company's proposed place in therapy. No comparative data are presented for ceftriaxone and there are only indirect comparative data for dalbavancin versus teicoplanin.
- The DISCOVER 1 and 2 studies excluded patients who had received antibiotics for Gram positive bacterial infections in the 14 days before starting treatment. However, the company proposes that dalbavancin will be used as second-line treatment in some patients[25].
- The Committee for Medicinal Products for Human Use considered that the VER001-9 study only provided supportive evidence for the licensed indication because of uncertainty about the severity of the infection and therefore the true need for intravenous therapy[2].
- All three studies included patients with MRSA infections, although the overall frequency of MRSA isolates was low in the DISCOVER 1 and 2 studies: < 30% of isolates[2]. Patients with diabetes are more likely to have severe infections requiring intravenous therapy. The DISCOVER 1 and 2 studies included patients with type 2 diabetes: 11.8% in the dalbavancin groups and 14.1% in the vancomycin and linezolid groups. It is unclear whether these figures reflect the population likely to be treated in Wales.
- For non-inferiority studies, the European Medicines Agency considers it necessary to have consistency in the outcomes between the clinically evaluable and intention-to-treat populations; therefore all treated populations in a study should be viewed as co-primary[2]. All the endpoints of the DISCOVER 1 and 2 studies and VER001-9 have been presented. Except for the result in the intention-to-treat population for the European Medicines Agency-defined primary endpoint in DISCOVER 1, these do show consistent results across the different endpoints[25,28].
- The network meta-analysis showed that dalbavancin was not significantly different to vancomycin, linezolid and teicoplanin in clinical success rates, and was associated with fewer adverse events and lower all-cause mortality. However, the analysis has a number of significant limitations. The studies included had different designs, different primary endpoints, used different definitions of skin and soft tissue infection and enrolled patients who had

different underlying diseases. Some of the treatments had small numbers of studies: there were three dalbavancin studies and one study of teicoplanin that could only be included by broadening the selection criteria. Some of the results from the network meta-analysis had wide credible intervals.

- Dalbavancin is given as either a single intravenous infusion or two infusions given one week apart, delivering 14 days of treatment in one or two doses[11]. This will allow patients to be discharged from hospital to recover at home, without having to attend hospital for daily antibiotic infusions. The long half-life of dalbavancin could pose a risk in the event of an adverse effect[2], although data to date show that the duration of adverse events for dalbavancin is similar to that seen for a pool of comparators, including vancomycin, linezolid and cephalosporin antibiotics[31].
- Dalbavancin is likely to require less monitoring than comparator medicines and has a low potential for interactions with other medicines[11].

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a cost-minimisation analysis (CMA) of dalbavancin (either 1,500 mg on Day 1 or 1,000 mg on Day 1 and 500 mg on Day 8 for intravenous infusion) compared with vancomycin and linezolid in adult patients with acute bacterial skin and skin structure infections (ABSSSI) who are hospitalised for their infection, require intravenous antibiotic treatment and are potentially eligible for early hospital discharge[1].

A decision tree model is used to estimate the difference in costs between dalbavancin and vancomycin and linezolid. The model adopts an NHS perspective and a time horizon of two months. The model assumes an initial therapy duration of 14 days; it is populated with data from the phase III dalbavancin clinical studies where possible[26,27,29].

Patients enter the model at initiation of therapy and continue on one of four possible pathways: (i) death from other causes (assumed at 3 days); (ii) switch to alternative agent, at the 3-day point, after which the second-line treatment continues for an additional 14 days; (iii) continue initial treatment pathway, discharged after 3 days to outpatient parenteral antimicrobial therapy (OPAT); or (iv) continue first-line treatment for full duration (14 days). All patients who do not die from other causes are assumed 'cured' in the model but may experience one recurrence within 28 days. The all-cause mortality rate in the clinical studies was low, at 0.6%, and is assumed unrelated to the study treatment. Patients experiencing a recurrence are treated in hospital for a further 14 days. The proportion of patients in the phase III studies[26,27,29] who were switched to the oral placebo was used as a proxy for the proportion of patients eligible for early hospital discharge.

Clinical parameters were taken from the pivotal studies[26,27,29], published literature[32] and expert opinion[33]. Costs considered in the model include antibiotic treatment costs, hospitalisation, OPAT and other healthcare visits as well as the cost of insertion, attention and removal of a peripherally inserted central catheter. Given the assumption of equivalent efficacy and safety, the costs related to concomitant medications and adverse events were considered to be the same and were excluded from the analysis. For patients receiving dalbavancin with an early hospital discharge, it was assumed that OPAT services would be used for the Day 8 infusion at a weighted average cost including delivery at an OPAT centre and at home by an OPAT nurse, district nurse or the patient. Unit costs were taken from published sources[34-36].

One-way sensitivity analyses are presented to estimate the effect of comparator dosages, recurrence rates, and uncertainties in unit costs on the results. Extensive scenario analyses present results for different comparators (daptomycin and teicoplanin), early discharge rate, and treatment duration.

4.2 Results

The results of the base case analysis are given in Table 4. Treatment with dalbavancin is less costly in the base case than vancomycin and linezolid treatment. The cost saving per patient with dalbavancin ranges from £2,164 (versus vancomycin) to £2,951 (versus linezolid).

Table 4. Results of the base case and scenario analyses

Scenario	Costs	Dalbavancin (£)	Vancomycin (£)	Difference (£)	Plausibility
Base case					
Dalbavancin versus vancomycin	Medicine acquisition costs	1,790	488	1,302	
	Other costs†	3,378	6,844	−3,466	
	Total costs	5,168	7,331	−2,164	
Base case					
Scenario	**Costs**	**Dalbavancin (£)**	**Linezolid (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus intravenous linezolid	Medicine acquisition costs	1,790	1,275	515	
	Other costs†	3,378	6,844	−3,466	
	Total costs	5,168	8,119	−2,951	
Scenario analysis: daptomycin is included as a comparator					
Scenario	**Costs**	**Dalbavancin (£)**	**Daptomycin (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus daptomycin	Medicine acquisition costs	1,790	971	819	While this scenario extends the comparator range, the plausibility depends on the routine use of these treatment options in practice. Clinical expert opinion sought by AWTTC suggests that daptomycin is rarely used in Wales.
	Other costs†	3,378	6,126	−2,748	
	Total costs	5,168	7,097	−1,929	
Scenario analysis: teicoplanin is included as a comparator					
Scenario	**Costs**	**Dalbavancin (£)**	**Teicoplanin (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus teicoplanin	Medicine acquisition costs	1,790	301	1,489	This is a plausible scenario as clinical expert opinion sought by AWTTC suggests that teicoplanin is in routine use in clinical practice.
	Other costs†	3,378	6,126	−2,748	
	Total costs	5,168	6,427	−1,259	
Scenario analysis: Patients treated with vancomycin are switched to oral linezolid upon early hospital discharge					
Scenario	**Costs**	**Dalbavancin (£)**	**Vancomycin (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus vancomycin followed by oral linezolid	Medicine acquisition costs	1,790	879	723	Less plausible than the base case as it is unlikely that all patients would be switched to oral linezolid. Clinical expert opinion sought by AWTTC suggests that patients would more likely be switched to intravenous ceftriaxone or teicoplanin upon early discharge than oral linezolid.
	Other costs†	3,378	3,704	−326	
	Total costs	5,168	4,583	585	

Scenario analysis: Patients treated with linezolid are switched to oral linezolid on early hospital discharge					
Scenario	**Costs**	**Dalbavancin (£)**	**Linezolid (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus intravenous linezolid followed by oral linezolid	Medicine acquisition costs	1,790	1,087	515	Less plausible than the base case as it is unlikely that all patients would be switched to oral linezolid. Clinical expert opinion sought by AWTTC suggests that intravenous linezolid is rarely used and that upon early discharge patients are more likely to be switched to intravenous ceftriaxone or teicoplanin than oral linezolid.
	Other costs[†]	3,378	3,704	−326	
	Total costs	5,168	4,791	377	
Scenario analysis: homogeneity in early hospital discharge rates between dalbavancin and vancomycin					
Scenario	**Costs**	**Dalbavancin (£)**	**Vancomycin (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus vancomycin	Medicine acquisition costs	1,790	488	1,302	The plausibility of this scenario depends on the feasibility of OPAT services delivering twice-daily infusions of vancomycin. Clinical expert opinion sought by AWTTC suggests that intravenous antibiotics with once-daily dosing are usually used in the OPAT setting.
	Other costs[†]	3,378	6,255	−2,877	
	Total costs	5,168	6,742	−1,574	
Scenario analysis: homogeneity in early hospital discharge rates between dalbavancin and linezolid					
Scenario	**Costs**	**Dalbavancin (£)**	**Linezolid (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus linezolid	Medicine acquisition costs	1,790	1,275	515	The plausibility of this scenario depends on the feasibility of OPAT services delivering twice-daily infusions of linezolid. Clinical expert opinion sought by AWTTC suggests that intravenous antibiotics with once-daily dosing are usually used in the OPAT setting.
	Other costs[†]	2,888	5,285	−2,397	
	Total costs	4,631	6,203	−1,572	

Scenario analysis: Intravenous vancomycin patients are switched to teicoplanin on early hospital discharge					
Scenario	**Costs**	**Dalbavancin (£)**	**Vancomycin (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus vancomycin	Medicine acquisition costs	1,790	321	1,469	This is a plausible scenario. Clinical expert opinion sought by AWTTC suggests that where MRSA is present, patients on intravenous therapy in hospital would usually be switched to teicoplanin upon early discharge.
	Other costs†	3,378	6,032	−2,654	
	Total costs	5,168	6,363	−1,195	
Scenario analysis: Intravenous linezolid patients are switched to teicoplanin on early hospital discharge					
Scenario	**Costs**	**Dalbavancin (£)**	**Linezolid (£)**	**Difference (£)**	**Plausibility**
Dalbavancin versus linezolid	Medicine acquisition costs	1,790	529	1,261	Clinical expert opinion sought by AWTTC suggests that where MRSA is present, patients on intravenous therapy in hospital would usually be switched to teicoplanin upon early discharge. They also confirmed that intravenous linezolid is rarely used.
	Other costs†	3,378	6,032	−2,654	
	Total costs	5,168	6,571	−1,403	
† Other costs consist of hospitalisation costs OPAT (outpatient parenteral antimicrobial therapy)					

The lower relative per-patient cost for dalbavancin is attributed to the difference in the early discharge rates between dalbavancin and the comparator antibiotics. The lower hospitalisation costs associated with dalbavancin are attributable to the higher percentage of patients able to be discharged early compared with the other intravenous antibiotics. This is due to higher resource use associated with OPAT; dalbavancin is given in one or two infusions over 8 days whereas the comparators are given as twice-daily infusions.

One-way sensitivity analyses found dalbavancin to be cost saving in all analyses. Net costs were between −£776 and −£3,659 for dalbavancin compared with vancomycin, and between −£1,563 and −£4,446 for dalbavancin compared with linezolid. Results were most sensitive to OPAT delivery costs and early hospital discharge assumptions. A range of scenario analyses were done alongside the base case; the most plausible and informative scenarios are reported in Table 4.

The results of the sensitivity and scenario analysis show that cost savings are most sensitive to the follow-on agent selection, with the comparators reporting lower overall costs than dalbavancin when oral linezolid was used. It is unlikely that all patients would be switched to oral linezolid.

4.3 AWTTC critique

The reliability of the CMA presented depends on the extent to which dalbavancin 500 mg for intravenous infusion is considered to be therapeutically equivalent to vancomycin and linezolid. The company justifies using a CMA on the basis that the supporting studies DISCOVER 1, DISCOVER 2 and VER001-9 showed dalbavancin

was non-inferior to vancomycin and linezolid, respectively. A network meta-analysis of studies in patients who are hospitalised due to ABSSSI and needed intravenous antibiotics showed broadly comparable efficacy and safety of dalbavancin versus comparators. The results of the CMA show that dalbavancin is cost-saving compared to intravenous vancomycin and intravenous linezolid.

Strengths of the economic analysis:

- The company has considered several comparators in its submission.
- The model appears sufficient to calculate meaningful results based on the CMA approach.
- The chosen time horizon seems appropriate considering the time-limited nature of the acute condition.

Limitations of the economic analysis:

- Although the company's submission relates to the licensed indication of dalbavancin for the treatment of ABSSSI in adults, the CMA restricts this indication to patients who are hospitalised for their infection, require intravenous antibiotic treatment, and are potentially eligible for early hospital discharge.
- The CMA approach is inappropriate because of uncertainty about the clinical equivalence between the comparators for several reasons:
    - The response rate to dalbavancin was lower compared with vancomycin and linezolid in the pivotal studies, which is likely to affect a patient's quality of life.
    - The CMA reports cost savings for dalbavancin which are mainly caused by earlier discharge from hospital. This implies an effect of dalbavancin on resource use and violates the assumption of equivalence required for a CMA to be appropriate. It would therefore be preferable to do a cost-utility analysis because the evidence does not support using a CMA.
    - A network meta-analysis done by the company concludes that there is no reason to assume that dalbavancin significantly differs to the other antibiotics with respect to efficacy. Whilst the analysis showed comparable efficacy of dalbavancin and its major comparators, this is not the same as demonstrating equivalence. There was also uncertainty surrounding some of the odds ratio estimates, and populations and underlying diseases differed markedly across the studies which would introduce bias.
    - The model assumes that 27% of patients continuing first-line treatment with the comparator treatments, who were eligible to be discharged early, remained in hospital due to OPAT capacity issues. This is based on a study conducted in Scotland[32]. Treatment patterns and patient pathways are based on data from NHS Greater Glasgow and Clyde, assuming that Welsh treatment patterns are similar to those in Scotland. Furthermore, the CMA assumes equivalence regarding health-related quality of life, survival, adherence and patient preference; the company does not provide evidence to support this assumption. Any differences will therefore introduce bias.
- The model uses the proportion of patients in the dalbavancin groups from the three trials (DISCOVER 1 and 2, and VER009-01) who were switched to oral placebo as a proxy for the proportion of patients who are eligible for early hospital discharge with dalbavancin. However, the criteria for early discharge are unclear and the use of a proxy might introduce bias and affect the appropriateness and generalisablitiy of the study results to routine practice.

- Due to a lack of available data, recurrence rates were based on assumptions which cannot be verified because no references were provided. Recurrence rates were assumed consistent across all intravenous medicines.
- Treatment patterns and patient pathways are based on data from NHS Greater Glasgow and Clyde and assume that Welsh treatment patterns are similar to those in Scotland. Any differences will therefore introduce bias.

4.4 Review of the published evidence on cost-effectiveness

A literature search by AWTTC did not identify any studies relevant to the cost-effectiveness of dalbavancin compared to vancomycin or linezolid in adults with ABSSSI who are hospitalised for their infection, need intravenous antibiotics and are potentially eligible for early hospital discharge.

5.0 BUDGET IMPACT

5.1 Context and methods

The population to be considered in the budget impact analysis is adults who are hospitalised for their infection, require intravenous antibiotic treatment and are potentially eligible for early hospital discharge in Wales. Prevalence is not considered in the budget impact model due to the short-term nature of the condition. The number of patients who would receive dalbavancin in Wales is based on the use of dalbavancin in Scotland. Internal sales data for dalbavancin reported that a total of 87 vials were used in the first 6 months after dalbavancin received a restricted recommendation for use in Scotland. Considering that every patient receives three 500 mg vials, this represents 29 patients treated with dalbavancin. Adjusting for the relative population size results in an estimated population coverage of 17 patients in Wales in Year 1. The company's internal forecasts assume an increase in patient numbers each year, resulting in an estimate of 178 patients in Year 5.

The treatment cost of dalbavancin is £1,629 for a course of three vials. The cost of the displaced medicines is assumed to be £565 based on a weighted cost of vancomycin, linezolid, daptomycin and teicoplanin. Other costs considered in the budget impact analysis are costs of stay in an infectious diseases unit, cost of intravenous treatment administration via OPAT, cost of other healthcare visits and costs of insertion, attention and removal of a peripherally inserted central catheter.

5.2 Results

The budget impact model shows net medicine acquisition costs of £18,394 in Year 1, rising to £190,525 in Year 5 (Table 5).

Table 5. Company-reported costs associated with use of dalbavancin

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Number of patients receiving dalbavancin	17	31	55	99	178
Medicine acquisition costs in a market without dalbavancin	£9,491	£17,705	£31,778	£56,207	£101,434
Medicine acquisition costs in a market with dalbavancin	£27,687	£50,487	£89,574	£161,233	£289,894
Net medicine acquisition cost	£18,196	£32,782	£57,796	£105,026	£188,460
Net supportive medicines costs	£198	£396	£532	£1,237	£2,065
Net medicine acquisition costs - including supportive medicines	**£18,394**	**£33,178**	**£58,328**	**£106,263**	**£190,525**

Use of dalbavancin produces savings in administration costs, OPAT and hospitalisation costs, resulting in a net budget impact of −£37,656 in Year 1, increasing to −£407,419 with an overall budget impact of −£868,076 over 5 years. The net resource implications are estimated as a saving of £56,050 in Year 1 rising to a saving of £407,419 in Year 5.

5.3 AWTTC critique

- Cost savings of dalbavancin are based on reduced length of hospital stays and reduced need for OPAT administration of intravenous antibiotics. These cost savings might be difficult to replicate in routine practice because the criteria for early discharge are unclear.
- All costs are derived from the economic model. As such, the limitations of the economic model apply to the budget impact estimates.

5.4 Comparative unit costs

Medicine acquisition costs of dalbavancin 500 mg and its main comparators are described in Table 6.

Table 6. Examples of medicine acquisition costs

Regimens	Example doses	Approximate costs per patient per course
Dalbavancin (Xydalba®) 500 mg vial for iv infusion	One infusion of 1,500 mg or two infusions (1,000 mg on Day 1 and 500 mg on Day 8)	£1,676.10
Vancomycin (Vancocin®) 500 mg vial for iv infusion	500 mg every 6 hours or 1,000 mg every 12 hours	£225.54 for 7 days £451.08 for 14 days
Linezolid (Zyvox®) 2 mg/ml for iv infusion	600 mg twice daily	£623 for 7 days £1,246 for 14 days
Teicoplanin (Targocid®) 200 mg or 400 mg vials for iv infusion, iv injection or im injection	6 mg/kg every 12 hours for three doses, then 6 mg/kg once daily	£58.56 for 7 days £109.80 for 14 days
Daptomycin (Cubicin®) 350 mg or 500 mg vials for iv infusion or injection	4 mg/kg every 24 hours 6 mg/kg every 24 hours	£434 for 7 days £868 for 14 days £619.99 for 7 days £1,239.98 for 14 days

iv: intravenous
im: intramuscular
See relevant Summaries of Product Characteristics for full licensed indications and dosing details[11,37-42].
Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of 10 April 2018[43], assuming vial wastage.
Costs of administration are not included.
Costs are based on a 75 kg patient.

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