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CADTH Reimbursement Recommendation

Dalbavancin (Xydalba)

Indication: For the treatment of adult patients with acute bacterial skin and skin structure infections, caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, *Streptococcus constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains)

Sponsor: Paladin Labs Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Xydalba?

CADTH recommends that Xydalba should be reimbursed by public drug plans for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA), only if certain conditions are met.

Which Patients Are Eligible for Coverage?

Xydalba should only be covered to treat patients who have known or suspected MRSA ABSSSI and are unlikely to adhere to outpatient antibiotic treatment or prolonged hospitalization.

What Are the Conditions for Reimbursement?

Xydalba should be negotiated so that it does not exceed the drug program cost of treatment with the least costly IV antibiotic reimbursed for the treatment of known or suspected MRSA ABSSSI.

Why Did CADTH Make This Recommendation?

- Evidence from 3 randomized controlled trials (RCT) demonstrated that patients with known or suspected gram-positive ABSSSI had similar likelihood of treatment response (based on signs and symptoms and need for new antibiotic treatment) and generally similar side effects with Xydalba as with vancomycin and IV linezolid each.
- Dalbavancin use would reduce the number of IV administrations in patients requiring IV antibiotic treatment, which addresses an unmet need of patients.
- Based on CADTH's assessment of the health economic evidence, Xydalba does not represent good value to the health care system at the public list price. The CADTH Canadian Drug Expert Committee (CDEC) determined that there is not enough evidence to justify a greater cost for Xydalba compared with other reimbursed IV antibiotics appropriate for the treatment of known or suspected MRSA ABSSSI (daptomycin, linezolid, and vancomycin).
- Based on public list prices, Xydalba is estimated to cost the public drug plans approximately $8 million over the next 3 years.

Additional Information

What Is ABSSSI?

ABSSSI are bacterial infections of the skin and associated tissues (e.g., cellulitis) and the severity ranges from non-severe to severe life-threatening infections affecting deeper tissue layers. Worldwide, the most common cause of ABSSSI is *Staphylococcus aureus,* which includes MRSA. In Canada, the estimated prevalence of skin and soft tissue infections requiring IV antibiotics is 0.39%.

Unmet Needs in ABSSSI

Treatments are needed that improve patient adherence, have fewer side effects, and reduce the number of IV administrations versus current treatment options.

How Much Does Xydalba Cost?

Treatment with Xydalba is expected to cost approximately $2,872 per patient.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dalbavancin be reimbursed for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Three double-blind, multi-centre, phase III, randomized controlled trials (RCTs) demonstrated that treatment with dalbavancin resulted in similar clinical benefit for patients with known or suspected gram-positive ABSSSI relative to vancomycin and IV linezolid, each with a possible switch to oral linezolid. Results from the DISCOVER 1 (N = 573) and DISCOVER 2 (N = 739) studies in patients with known or suspected gram-positive ABSSSI showed that the 2-dose dalbavancin regimen was noninferior to vancomycin in the percentage of patients with clinical response at 48 to 72 hours after treatment initiation (noninferiority margin of 10% for the mean difference). Results for clinical response at later time points were supportive of noninferiority of dalbavancin versus vancomycin. Results from the VER001 to 9 study (N = 854) in patients with known or suspected gram-positive complicated skin and skin structure infections showed that the 2-dose dalbavancin regimen was noninferior to IV linezolid in the percentage of patients with clinical response 28 days after treatment initiation (noninferiority margin of 12.5% for the mean difference). Results for clinical response at 14 days after treatment initiation were supportive of noninferiority of dalbavancin versus IV linezolid. Vancomycin and IV linezolid are appropriate treatments when MRSA infection is known or suspected, but are not the standard of care for methicillin-sensitive *Staphylococcus aureus* MSSA infections and other gram-positive ABSSSI, where a narrower spectrum of antibacterial drug action is preferred. Therefore, the comparative efficacy of dalbavancin versus treatments appropriate for non-MRSA ABSSSI is unknown. The adverse event (AE) profile was generally similar between dalbavancin and the comparator in the 3 RCTs.

According to the clinical expert, there is a need for treatments that improve patient adherence, have fewer side effects than current options, and reduce the number of IV administrations (with their associated health care resource utilization, patient travel, and potential complications). CDEC noted that dalbavancin use would reduce the number of IV administrations in patients requiring IV antibiotic treatment.

Using the sponsor-submitted price for dalbavancin and publicly listed prices for all other drug costs, dalbavancin was more costly compared to vancomycin and all other included IV antibiotic treatments. Due to the limitations in the data concerning infection-related hospital days, the magnitude of comparative effectiveness between treatments was unknown. As such, dalbavancin should be no more costly than the least costly IV antibiotic treatment for adult patients with known or suspected MRSA ABSSSI.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with dalbavancin should only be reimbursed for treatment in adult patients with all of the following: 1.1. Known or suspected MRSA ABSSSI 1.2. High risk of nonadherence to outpatient antibiotic treatment or high risk of nonadherence to prolonged hospitalization	Dalbavancin was compared with vancomycin and linezolid in the DISCOVER 1, DISCOVER 2, and VER001 to 9 studies and these drugs are the current standard of care for known or suspected MRSA ABSSSI, and not for other ABSSSI where a narrower spectrum antimicrobial can be used. The comparative efficacy of dalbavancin vs. treatments for non-MRSA ABSSSI is unknown. Due to the single-dose option of dalbavancin, treatment with dalbavancin is more likely to benefit patients at risk of nonadherence to outpatient antibiotic treatment with other therapies or prolonged hospitalization. Improved adherence in these patients may reduce the risk of treatment failure.	Ideally, a microbiological sample should be taken and culture results available to guide treatment. However, CDEC acknowledged that this is not a consistent practice and that in many cases MRSA status will be unknown, or results may not become available until after initiation of therapy. CDEC also acknowledged that the determination of high risk of nonadherence to outpatient antibiotic treatment or prolonged hospitalization would be up to the clinical judgment of the treating physician.
Pricing		
2. Dalbavancin should be negotiated so that it does not exceed the drug program cost of treatment with the least costly IV antibiotic reimbursed for the treatment of known or suspected MRSA ABSSSI.	There is insufficient evidence to justify a price premium for dalbavancin over other currently reimbursed IV antibiotics appropriate for the treatment of known or suspected MRSA ABSSSI (daptomycin, linezolid, and vancomycin).	–

ABSSSI = acute bacterial skin and skin structure infections; CDEC = Canadian Drug Expert Committee; MRSA = methicillin-resistant *Staphylococcus aureus*.

Discussion Points

- CDEC emphasized the importance of limiting the potential for the development of antimicrobial resistance by minimizing antimicrobial use where possible. Therefore, CDEC strongly encourages the oversight of dalbavancin use by an antimicrobial stewardship program where possible.
- While subgroup analyses in the 3 RCTs suggested that efficacy in MRSA ABSSSI was consistent with that in the full study populations, the subgroup analyses were not adjusted for multiplicity and not a part of sample size considerations for the trials.
- One indirect treatment comparison (ITC), a published network meta-analysis (NMA) included in the sponsor's submission, evaluated the comparative efficacy and safety of dalbavancin versus IV antibiotics for the treatment of ABSSSI. There was a high degree of uncertainty in comparative efficacy and safety due to the serious limitations of the NMA,

which included high clinical heterogeneity in study design and patient characteristics, a sparse evidence network, and wide credible intervals. While the results favoured dalbavancin for certain safety outcomes in some comparisons, conclusions could not be drawn due to the limitations.

- Dalbavancin only requires 1 or 2 doses compared with twice daily administration of vancomycin or linezolid over several days and therefore reduces the number of required IV administrations and may offer benefit in terms of treatment adherence in patients at risk of nonadherence to currently available treatment options. However, there was no high-quality evidence measuring the impact of the 1- or 2-dose dalbavancin regimen in clinical practice on treatment adherence, health care resource utilization, need for patient travel, and complications of IV administration.
- While results from 2 pragmatic studies with a pre-post design (ENHANCE and ADVANCE) suggested that introducing a hospital critical pathway that included dalbavancin in patients with ABSSSI was associated with a reduction in mean total and infection-related hospital days (but no reduction within the subgroup of admitted patients in ADVANCE), conclusions could not be drawn due to serious limitations that included risk of time-related confounding, performance bias, and attrition bias.
- The sponsor-submitted pharmacoeconomic model assumed equal treatment efficacy for all IV antibiotics, including dalbavancin, for both severe and non-severe disease. The model was highly sensitive to changes in the hospital discharge rate, such that the increased cost of dalbavancin could be outweighed by reductions in hospital costs. However, the data submitted by the sponsor were insufficient to demonstrate such a reduction and CDEC considered it appropriate to make no assumption about differential efficacy.
- The sponsor submitted a scenario analysis examining the use of dalbavancin in unhoused people whose disease course may be more severe. The uncertainty around the estimated incremental effectiveness, and the limitations of the submitted evidence, meant that conclusions could not be drawn about this population. It should be noted, however, that unhoused people likely require more complex care than those who are comfortably housed, and then face additional disease burden due to comorbidities and unstable access to health care services. This additional complexity and burden raise important cost-effectiveness and equity concerns.
- Clinical expert input suggested that severe and non-severe ABSSSI does not have a consistent clinical definition. Non-severe cases may be managed using oral antibiotic treatments. The sponsor omitted oral antibiotics from their pharmacoeconomic modelling, and the cost-effectiveness of dalbavancin compared to non-severe ABSSSI management is therefore unknown (though oral antibiotic drug costs are orders of magnitude lower than the cost of dalbavancin).

Background

ABSSSIs are bacterial infections of skin and associated tissues. ABSSSIs include cellulitis, erysipelas, wound infection and major cutaneous abscesses. Worldwide, the most common cause of ABSSSI is *Staphylococcus aureus* (S. *aureus*), including methicillin-resistant *S. aureus* (MRSA). In Canada, the estimated prevalence of ABSSSIs requiring IV antibiotics is 0.39%. Severity ranges from non-severe infections to severe life-threatening infections affecting deeper tissue layers. ABSSSI caused by MRSA are associated with increased risk of mortality, longer hospital length of stay (LOS), and higher health care costs than non-MRSA infections.

The current standard of therapy for ABSSSI in Canada is a cephalosporin for MSSA infections (i.e., IV cefazolin, IV ceftriaxone, or oral cephalexin) and IV vancomycin, IV daptomycin, or oral or IV linezolid for MRSA infections (daptomycin and linezolid being rarely used). For severe ABSSSI, treatment would include IV piperacillin/tazobactam or IV ertapenem. The goals of therapy are prevention of mortality, improvements in accessibility and compliance, and reducing risk of IV related complications, hospital visits, and health care costs. In many cases, the microbiological cause of ABSSSI is unknown as a microbiological specimen is not obtained. Among outpatients, lack of compliance may contribute to failure of initial therapy, which may result in hospitalization.

Dalbavancin has been approved by Health Canada for treatment of adult patients with ABSSSI, caused by susceptible isolates of the following gram-positive micro-organisms: *Staphylococcus aureus (*including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group* (including *Streptococcus anginosus, Streptococcus intermedius, Streptococcus constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains). Dalbavancin is a semisynthetic bactericidal lipoglycopeptide active against susceptible strains of gram-positive bacteria. It is available as a 500 mg vial for IV infusion and the dosage recommended in the product monograph is 1,500 mg, administered either as a single dose or as 1,000 mg followed 1 week later by 500 mg over 30 minutes by IV infusion.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a review of the 4 RCTs in adult patients with ABSSSI
- a review of 1 ITC
- a review of 2 pragmatic trials with a pre-post design
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with ABSSSI
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert noted many treatment gaps in patients with ABSSSI. This included current IV treatment being expensive and complicated (potentially requiring nursing effort, peripherally inserted central catheter (PICC) line insertion, repeated visits, and automated IV pumps), risk of IV line complications, poor patient adherence to treatment, difficulty obtaining a microbiological culture, and toxic effects from current standard of care (e.g., IV vancomycin, which requires therapeutic monitoring). Sometimes, given the difficulty in obtaining a swab to identify the pathogen, the diagnosis may be incorrect and delay the treatment

process. In addition, patients may be misdiagnosed with ABSSSI and given unnecessary treatment. In terms of access, people in remote areas or Indigenous groups may have poor or limited access to IV treatment and may face geographic barriers accessing treatment after discharge.

According to the clinical expert, dalbavancin could change the current treatment paradigm given its unique pharmacokinetics and ease of use compared to other treatments. Dalbavancin would be considered a first-line treatment and would replace current IV antibiotic treatments for ABSSSI caused by gram-positive bacteria (unless oral antibiotic treatment was available). In the opinion of the clinical expert, there would be no reason to try other treatments before dalbavancin. Given that dalbavancin does not require repeat IV infusion, PICC line placement, and therapeutic drug monitoring, it is much easier to access than other standards of therapy and may have better patient satisfaction. In addition, dalbavancin could prevent repeat visits, admission, and poor adherence, which is seen with other therapies. According to the clinical expert, patients best suited for treatment with dalbavancin include patients with MRSA infection, people who inject drugs, patients identified by physician assessment at presentation, and home IV candidates who are clinically stable, have mild to moderate infection, are competent, and have access to a nearby hospital. Patients least suited for dalbavancin include patients with infections that require surgical debridement, and patients with polymicrobial infections. According to the clinical expert, response in a trial setting is best assessed using the FDA outcome criteria at 48 to 72 hours: alive, and 20% reduction in affected area, and no rescue treatment. In clinical practice, there are typically daily assessments, which may not be necessary; also, assessment may be highly variable between physicians (e.g., determining time to resolution of redness). Patients can be re-treated, typically around day 8, if there is no response. However, physicians should investigate reasons for non-response and adjust treatment plan accordingly.

The clinical expert indicated that dalbavancin could be given in any setting in which there is IV access (e.g., emergency room [ER], long-term care, hospital, clinic, or home visit). Dalbavancin does not require a specialist for prescription, although its use should be regulated carefully by an antimicrobial stewardship committee. Treatment should not be used off label without trial evidence. The clinical expert added that trials should be done in osteomyelitis, endocarditis, abscess, prosthetic joint infection, pneumonia, and meningitis.

The clinical expert also noted that dalbavancin has some potential harms. If an allergic reaction occurred, there would be no way to withdraw the drug. Also, the convenience of dosing of dalbavancin could increase unnecessary treatment by increasing treatment of the wrong diagnosis, failure to change treatment after culture results are received, increasing IV treatment when oral treatment would be adequate, or increasing unnecessary prophylaxis. According to the clinical expert, there may be concerns related to antimicrobial resistance with the use of dalbavancin if used inappropriately; with dalbavancin there is prolonged duration of selection toward antimicrobial resistance among human gut flora. Antimicrobial resistance is associated with enormous cost to the Canadian health system and mortality among Canadians; therefore, antimicrobial use must be minimized, both in spectrum of action and duration of treatment, to reduce antimicrobial resistance.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Comparator drugs are listed in various ways in many jurisdictions, ranging from non-benefit to restricted access to full benefit.	This was a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Can the drug be given again to patients who may not have had full response, or the infection returns? Can treatment be repeated? If so, what would be the appropriate timing of re-treatment?	CDEC agreed with the clinical expert that infection can recur and patients can be re-treated with dalbavancin at the time of recurrence. If patient fails to clear the infection after a single dose of dalbavancin, a repeat dose could be given.
Considerations for discontinuation of therapy	
Is there a time period required before repeating treatment, if necessary?	CDEC agreed with the clinical expert that clinicians would wait for the drug to clear from the patient's body, which is typically 5 to 7 days after administration. If there was treatment failure, they noted that the treating physician would reflect on the reasons why treatment is not working.
Considerations for prescribing of therapy	
Access to a hospital or infusion clinic or the ability to provide infusion services as an outpatient may be necessary.	This was a comment from the drug programs to inform CDEC deliberations.
Generalizability	
There may be requests to use dalbavancin for infections in the pediatric population. Dalbavancin is currently under review in US for this population.	CDEC noted that the pediatric population falls outside of the Health Canada–approved indication.
Could this drug be used off label for infections other than ABSSSI, but with susceptible gram-positive organisms (e.g., osteomyelitis, endocarditis etc.)?	The clinical expert indicated that there would be great demand for dalbavancin to be used off label for other infections due to the convenience of its use. The expert was therefore hopeful that there could be additional trials for dalbavancin in any serious gram-positive infection (e.g., diabetic foot infection, endocarditis, prosthetic joint infection). CDEC acknowledged the clinical expert's input and noted that dalbavancin should not be reimbursed for off-label use as there is no evidence to support this use. CDEC also emphasized the importance of having effective antimicrobial stewardship processes in place to prevent off-label use of dalbavancin.
Care provision issues	
Drug may need to be infused in hospital or infusion clinic or have ability to infuse in outpatient setting.	This was a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Outpatient infusion services may be associated with an extra cost. Being a one-time dose, where will dalbavancin fit in the health care system? Will it be funded by the health authorities or drug plans?	The clinical expert anticipated that most patients would use the ER or outpatient infusion services, and the proportion of patients accessing through each route would depend on how care is delivered in different locations.

Implementation issues	Response
	CDEC acknowledged the clinical expert's input and noted that the distribution between funding sources may vary across jurisdictions.
This therapy may require resources and/or facilities that may not be available in all locations. The drug plans may need to cover travel expenses for eligible patients.	This was a comment from the drug programs to inform CDEC deliberations.
Relevant comparators have been around for some time and are much less expensive.	This was a comment from the drug programs to inform CDEC deliberations.
Only one or 2 infusions are needed, therefore there is less time in hospital and less associated costs if successful in treating the infection. The cost of the drug itself ($957.1679 per vial) is significantly higher than the IV comparators that are used for 5 to 10 days. It has a better safety profile, less serious adverse effects, less demand for monitoring, and less infusions needed. The cost-effectiveness model submitted by the manufacturer showed dalbavancin to be dominant to all comparators in severe ABSSSI treatment. In non-severe infection, it was dominant to vancomycin IV, linezolid IV, and daptomycin IV. In kidney dysfunction patients it was dominant to all IV treatments except ceftriaxone.	This was a comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Four RCTs were included in this review, DISCOVER 1, DISCOVER 2, DUR001 to 303, and VER001 to 9. The first 3 RCTs were considered pivotal trials by Health Canada. DISCOVER 1, DISCOVER 2, and DUR001 to 303 were sponsored by Durata Therapeutics and VER001 to 9 was sponsored by Vicuron Pharmaceuticals Inc.

DISCOVER 1 (N = 573) and DISCOVER 2 (N = 739) were phase III, multi-centre, 1:1 randomized, double-blind (DB), noninferiority studies comparing the efficacy and safety of dalbavancin to vancomycin (with a possible switch to oral linezolid) in patients with known or suspected gram-positive ABSSSI. The primary objective in both trials was to compare clinical efficacy 48 to 72 hours after study drug initiation between dalbavancin and a vancomycin and linezolid regimen. Clinical response was defined as no increase in lesion size, absence of pyrexia at 48 to 72 hours in the ITT population, and no new systemic antibacterial treatment for gram-positive ABSSSI. In both trials the key secondary objectives included the following: clinical response at 48 to 72 hours post-study drug initiation based on measurements of ABSSSI lesion size (≥ 20% reduction in lesion area); clinical efficacy at day 14 to 15 post-study drug initiation (end of treatment [EOT] visit) based on lesion size, local signs, temperature and receipt of non-study antibiotics; and clinical efficacy at the day 28 short-term follow-up

(SFU) visit based on lesion size, local signs, temperature and receipt of non-study antibiotics. Patients assigned to dalbavancin received a 1,000 mg dose on day 1 followed by a 500 mg dose on day 8 with a possible switch to oral placebo (if switching criteria were met) for a total duration of 14 days. Patients assigned to IV vancomycin received at least 3 days of therapy with the option to switch to oral linezolid to complete 10 to 14 days of therapy. For both treatment arms, the total course of therapy (IV and oral) was 14 days. Treatment was initiated on day 1 and efficacy and safety assessments took place on days 2, 3, 4, and 8 as well as at the EOT (day 14) visit. Following the EOT visit, patients were to return for SFU at day 28 and long-term follow-up (LFU) at day 70 (2 months after the EOT visit).

DUR001 to 303 (N = 698) was a phase III, multi-centre, 1:1 randomized, DB, noninferiority study designed to compare single-dose versus 2-dose IV dalbavancin regimens in patients with known or suspected gram-positive ABSSSI. The primary objective of this study was to compare the efficacy of treatment with a single dose of dalbavancin 1,500 mg to treatment with a 2-dose regimen of dalbavancin (1,000 mg on day 1 followed by 500 mg on day 8) at 48 to 72 hours after initiation of treatment. Clinical response was defined as the patient being alive, not receiving rescue therapy for ABSSSI, and having at least 20% decrease in lesion area. The secondary objectives of this study were clinical status at day 14 to 15 (EOT visit) and day 28 (± 2 days) post-study drug initiation and safety. Other objectives looked at health care resource utilization, including hospital LOS. Patients in the single-dose group received a single dose of dalbavancin IV on day 1, and a dalbavancin-matching placebo on day 8. Patients randomly assigned to the 2-dose dalbavancin group received the first dose of dalbavancin on day 1, and the second dose of dalbavancin on day 8. Treatment was initiated on day 1 and efficacy and safety assessments took place on day 3 to 4, day 8, day 14 to 15 (EOT visit), and day 28 (final visit).

VER001 to 9 (N = 854) was a phase III, multi-centre, 2:1 randomized DB noninferiority study that aimed to determine whether dalbavancin was noninferior to IV linezolid (with a possible switch to oral linezolid) in adult patients with complicated skin and skin structure infections (SSSIs) due to gram-positive pathogens based on clinical response, defined as survival status, temperature and no rescue therapy. The primary objective of VER001 to 9 was to compare the clinical efficacy and safety of dalbavancin (2-dose regimen) with that of a linezolid regimen in the treatment of adult patients with complicated SSSIs due to gram-positive pathogens. A clinical response of success was defined as sufficient resolution of the local and systemic signs and symptoms of SSSI such that the patient did not receive new systemic antibacterial treatment for SSSI. Additional objectives included hospital utilization and LOS. Treatment was initiated on day 1 and efficacy and safety assessments took place on day 4, day 8, within 3 days following treatment completion on day 14 (EOT), day 28 (test of cure [TOC]), and on day 39 (LFU).

In DISCOVER 1, DISCOVER 2, and DUR001 to 303, patients were aged 18 to 85 years with a known or suspected ABSSSI (major cutaneous abscess, surgical site or traumatic wound infection, or cellulitis) accompanied by at least 75 cm^2 of erythema, at least 2 signs of ABSSSI (purulent drainage or discharge, fluctuance, heat or localized warmth, tenderness to palpation, and swelling or induration), at least 1 systemic sign of infection, and infection severity requiring a minimum of 3 days of IV therapy. The most common infection type was cellulitis (47.3% to 54.2% of patients), followed by major cutaneous abscess (25.0% to 30.2%) and wound infection (18.2% to 26.4%). Of patients with a known pathogen, 16.7% to 28.8% had an MRSA infection and 41.8% to 58.0% had an MSSA infection.

In VER001 to 9, inclusion and exclusion criteria were similar to the those of the other 3 trials, though no threshold was set for the size of erythema and threshold for increased WBCs was at least 10,000/mm^3. Major cutaneous abscess was the most common infection type (30.4% to 33.3%), followed by cellulitis (27.5% to 29.7%) and wound infection (19.2% to 21.2%), and 62.5% to 64.3% were hospitalized at study entry. Of patients with a known pathogen, 88.8% to 90.6% had a *Staphylococcus aureus* infection and 51% had a MRSA infection.

Efficacy Results

Overall, the 2-dose regimen of dalbavancin was considered noninferior to the comparator regimens regarding clinical response at 48 to 72 hours across the pivotal trials and at day 28 in VER001 to 9; In addition, single-dose dalbavancin was noninferior to 2-dose dalbavancin.

Clinical Response or Success

In DISCOVER 1, clinical response rate at 48 to 72 hours was 83.3% in the dalbavancin group versus 81.8% in the vancomycin group (1.5% treatment difference; 95% confidence interval [CI], −4.6 to 7.9). The lower limit of the 95% CI for the treatment difference was higher than the pre-specified noninferiority margin of −10%. Therefore, noninferiority of dalbavancin to vancomycin was concluded. The proportion of patients in the ITT population with clinical success at EOT (day 14) was similar between groups, with 81.9% in the dalbavancin group versus 86.7% in the comparator group for a between-group difference of −4.8% (95% CI, −10.7% to 1.3%). The proportion of patients with clinical success at day 28 was 83.7% for dalbavancin versus 88.1% for comparator (−4.4% treatment difference; 95% CI, −10.1% to 1.4%).

In DISCOVER 2, clinical response rate at 48 to 72 hours was 76.8% in the dalbavancin group versus 78.3% in the vancomycin group (−1.5% treatment difference; 95% CI, −7.4% to 4.6%). The lower limit of the 95% CI for the treatment difference was higher than the pre-specified noninferiority margin of −10%. Therefore, noninferiority of dalbavancin to vancomycin was concluded. In addition, clinical response at EOT (day 14 to 15) in the clinically evaluable (CE) population was consistent with the ITT population with a treatment difference of 2.8% (95% CI, −6.7% to 0.7%) in favour of the comparator. At EOT (day 14), there was 88.7% in the dalbavancin group versus 85.6% in the comparator group with clinical success for a between-group difference of 3.1% (95% CI, −1.8% to 8.0%). At day 28, there was 88.1% in the dalbavancin group versus 84.5% in the comparator group with clinical success for a between-group difference of 3.6% (95% CI, −1.1% to 8.9%).

Sensitivity analyses conducted in both DISCOVER 1 and 2 were consistent with the results of the primary analysis.

In DUR001 to 303, clinical response rate at 48 to 72 hours was 84.2% in the 2-dose arm of dalbavancin versus 81.4% in the single dose arm with a between-group difference of 2.9% (95% CI, −8.5% to 2.8%). The lower limit of the 95% CI for the treatment difference was higher than the pre-specified noninferiority margin of −10%. Therefore, noninferiority of 1-dose to 2-dose dalbavancin was concluded. At EOT (day 14) and at day 28, the treatment difference for the single-dose versus 2-dose regimens was −0.9% (95% CI, −6.3% to 4.6%) and 0.6% (95% CI, −6.0% to 4.8%), respectively.

Clinical response at 48 to 72 hours across subgroups (MRSA versus MSSA; infection type) showed similar clinical response rates across all trials and groups.

In VER001 to 9, clinical response was assessed at EOT (day 14) and TOC (day 28) in the ITT population of the study. Clinical response rate at TOC, the primary end point, was 76.5% in the dalbavancin arm and 82.7% in the linezolid arm. The treatment difference was −6.15% (95% CI, −12.03% to −0.27%). The lower limit of the 95% CI for the treatment difference of −6.5% remained above the pre-specified noninferiority margin of −12.5%. Therefore, noninferiority of dalbavancin to linezolid was claimed. In terms of clinical response at EOT, results were consistent with those seen at TOC, with 80.6% in dalbavancin versus 86.9% in linezolid deemed clinical successes in the ITT analysis. Clinical response was also evaluated in the CE population at TOC (Day 28) and results were consistent with that of the ITT population (−2.21% treatment difference, 95% CI, −7.28% to 2.86%).

Clinical Failure at End of Treatment

In DISCOVER 1, a total of 38 patients (13.2%) in the dalbavancin treatment group and 29 (10.2%) patients in the vancomycin treatment group in the ITT population were clinical failures at EOT (day 14). The most commonly reported reasons for clinical failure were that local signs of fluctuance and localized heat/warmth had not resolved (84.2% of patients on dalbavancin and 79.3% of patients on vancomycin treatment with treatment failure, respectively), local signs of tenderness to palpation and swelling/induration were worse than mild (23.7% and 34.5%, respectively), and the patient received a new non-study systemic antibacterial treatment (34.2% and 13.8% respectively).

In DISCOVER 2, a total of 32 (8.6%) patients in the dalbavancin treatment group and 33 (9.0%) patients in the vancomycin treatment group in the ITT population were clinical failures at EOT. The most commonly reported reasons for clinical failure at the EOT in both treatment groups were the same as DISCOVER 1: local signs of fluctuance and localized heat/warmth had not resolved (53.1% of those on dalbavancin and 60.6% of those on vancomycin/linezolid treatment with treatment failure, respectively), local signs of tenderness to palpation and swelling and/or induration were worse than mild (34.4% and 48.5%, respectively), and the patient received a new non-study systemic antibacterial treatment (28.1% and 42.4%, respectively).

In DUR001 to 303, 42 (12.0%) patients on single dose dalbavancin and 36 (10.3%) patients on 2-dose dalbavancin in the ITT population were clinical failures at EOT. The most common reasons for clinical failure were: lesion size did not decrease from baseline (73.8% on 1-dose and 66.7% on 2-dose with treatment failure), local signs of tenderness to palpation and swelling and/or induration were worse than mild (21.4% on 1-dose and 19.4% on 2-dose), and the patient received a new non-study systemic antibacterial treatment (21.4% on 1-dose treatment and 16.7% on 2-dose treatment).

Harms Results

In DISCOVER 1 and 2, the incidence of patients with treatment-emergent AEs (TEAEs) was lower in the dalbavancin treatment group than in the vancomycin/linezolid treatment group (34.9% versus 39.4% in DISCOVER 1 and 31.3% versus 36.8% in DISCOVER 2). Across the pivotal trials, the number and type of TEAEs were similar between groups, with the most commonly reported TEAEs being headache, nausea, hypertension, and rash. In DISCOVER 2, the TEAEs reported were similar to DISCOVER 1. In DUR001 to 303, the incidence of TEAEs were similar between the single- versus 2-dose dalbavancin treatment regimens (20.1% versus 19.9%). The most common (reported in at least 2% of patients) TEAEs in the single-dose and 2-dose treatment groups were nausea (3.4% versus 2.0%), headache (1.7% versus 1.2%), and vomiting (1.7% versus 0.9%). In VER001 to 9, the most commonly reported

(at least 2% of patients) TEAEs throughout the entire study period for both the dalbavancin and linezolid, respectively were nausea (3.2% versus 5.3%), diarrhea (2.5% versus 5.7%) and headache (1.9% versus 1.8%).

In DISCOVER 1, treatment-emergent serious adverse events (SAEs) were less commonly reported in the dalbavancin treatment group than in the comparator group (1.8% versus 4.2%, respectively). In DISCOVER 2, there were similar numbers of treatment-emergent SAEs between treatment groups (3.3% versus 3.8%, respectively). In DUR001 to 303, the percentages of patients with SAEs were similar across treatment groups (2.0% in the single-dose group versus 1.4% in the 2-dose group). In VER001 to 9, there were similar rates of SAEs with 7.5% in the dalbavancin and 8.4% in the linezolid group.

The proportion of patients who discontinued treatment due to AEs was similar in the 2 treatment groups across the RCTs (1.8% or less in all groups).

The number of deaths were similar between groups in all trials (0.7% of each group or less), except for DISCOVER 1 where there were deaths in 1.8% of the vancomycin/linezolid group and none in the dalbavancin group. The most common notable harms were infusion related reactions (1.8% or less of each group), rash or hypersensitivity reactions (0.8% to 2.1% of each group in the pivotal trials), and hepatic adverse event (0.8% to 2.1% in DISCOVER 1 and 2).

Critical Appraisal

Internal Validity

The noninferiority design was adequately powered, and the threshold used (−10% to −12.5%) was justified. According to the clinical expert consulted by CADTH, the 10% noninferiority margin is somewhat wide, but a loss of approximately 5% in clinical benefit would not be too concerning for the treatment of ABSSSI. Also, the expert indicated that while vancomycin is expected to be efficacious in this population (especially in those with MRSA), linezolid is a bacteriostatic rather than bactericidal drug and may not be as efficacious as other available options. While the dosing of vancomycin aligned with the recommended dose for this population, it may not have been the most appropriate comparator given that majority of patients with *S. aureus* infections were MSSA and not MRSA. According to the clinical expert, more appropriate drugs for patients with MSSA include cephalosporins such as IV ceftriaxone or oral cephalexin.

The primary outcome in DUR001 to 303 corresponds to the primary efficacy end point recommended in the FDA draft guidance for developing drugs for ABSSSIs, and the primary outcome in DISCOVER 1 and DISCOVER 2 were also similar. The primary outcome for DISCOVER 1 and DISCOVER 2 also considered resolution of fever and did not require a decrease in lesion size for clinical response, which is more aligned with how patients are assessed in clinical practice as the requirement for a 20% reduction in lesion area (part of the FDA-recommended outcome) is arbitrary and fever, white blood cell count, and pain are typically assessed. The clinical expert noted that the outcomes for VER001 to 9 were less well-defined. Overall, the expert considered the efficacy outcomes in the 4 studies and follow-up to be appropriate for advising on the use of dalbavancin in patients with ABSSSI.

Treatment compliance was generally similar between groups, and higher in the dalbavancin group compared to other IV therapies and the single-dose regimen versus 2-dose. The use of concomitant antibiotic therapy was similar between groups across all trials, hence bias toward treatment outcome is low. Subgroup analyses did not include statistical testing

and were limited in numbers; hence results should be considered exploratory. Overall, the subgroup results were similar to the primary analysis.

External Validity

The clinical expert consulted by CADTH, agreed that the baseline patient characteristics of the pivotal trials and VER001 to 9 were reflective of patients they see in Canadian clinical practice for the present indication. Although the majority of patients in each study were enrolled in trial sites from the US and Europe, the population enrolled in the trial was consistent with the population expected to be treated in Canadian clinical practice. In general, lesion size was quite large across all trials, (e.g., ~300 cm^2 up to ~750 cm^2), which is indicative of more severe ABSSSI; this may limit generalizability to populations with smaller lesion sizes. Furthermore, the subgroup analyses (e.g., bacteremia, infection type, MRSA status) had no statistical comparisons and smaller sample sizes, which limits the generalizability to a broader population. According to the clinical expert, the concomitant medications used in the trial were reflective of the that seen in Canadian clinical practice.

Indirect Comparisons

Description of Studies

The authors of the published ITC included in the sponsor's submission conducted a systematic review and used a Bayesian NMA to evaluate the relative clinical and safety efficacy of IV antibiotics for the treatment of ABSSSI in adult patients. The efficacy outcomes were clinical treatment success and microbiological success, and the safety outcomes were discontinuation due to AEs and SAEs, patient experiencing any AEs, patient experiencing any SAEs, and all-cause mortality.

Efficacy Results

The NMA showed no evidence for a difference in clinical success between dalbavancin and vancomycin (odds ratio [OR] = 0.99; 95% credible interval [CrI], 0.68 to 1.51), linezolid (OR = 0.69; 95% CrI, 0.41 to 1.00), or daptomycin (OR = 1.05; 95% CrI, 0.61 to 2.10).

Safety Results

The ITC reported that dalbavancin is associated with a lower likelihood of experiencing an AE than linezolid, a lower likelihood of experiencing an SAE than vancomycin and daptomycin, and a lower risk of all-cause mortality than vancomycin, linezolid and tigecycline. However, the credible intervals were wide, particularly for SAEs and mortality.

Critical Appraisal

The ITC had several limitations including high clinical heterogeneity in study design (e.g., patient selection criteria, definitions of response, and timing of assessment) and in patient characteristics. High statistical heterogeneity was also present within the pairwise meta-analyses. The structure of the network was star-shaped with 1 closed loop, with some contrasts represented by 1 or 2 trials. Due to small numbers of trials included in the NMA, the ability to estimate between-trial variance was limited. As a result, analyses with uncommon events such discontinuations due to adverse events and severe adverse events, would likely produce imprecise estimates. Furthermore, there were limitations due to the lack of reporting certain items that would better inform on the certainty of the indirect evidence; the authors did not report risk of bias when pooling the studies, and the authors did not adequately report sensitivity and subgroup analysis to investigate the root of heterogeneity or conduct a

meta-regression that would adjust for effect modifiers that may influence the results. Overall, there was substantial uncertainty around the ITC due to imprecision and risk of bias.

Other Relevant Evidence

Description of Studies

The ENHANCE and ADVANCE were pre-post pragmatic studies that provide further evidence on the efficacy (hospital LOS and hospital admission rate) and safety of dalbavancin in patients with ABSSSI.

The pre-post pragmatic study, ENHANCE, was conducted to estimate the difference in infection-related total admitted hospital days during initial care (the period between date of enrolment to 10 to 14 days) and follow-up (the period between end of initial care to 30 days) between patients with ABSSSI who received care before (pre-period) and after (post-period) the implementation of a critical pathway that was developed for the management of patients with ABSSSI who were admitted to the hospital. The intervention was the critical pathway that comprised of identifying patients using criteria that were developed based on guidelines on the management of ABSSSI in the hospital setting and outpatient parenteral antibiotic therapy, and administering dalbavancin to patients who met the criteria and were subsequently discharged to an outpatient setting at the discretion of the treating physician. During the pre-period, only the first component of the critical pathway was implemented and usual care for ABSSSI was initiated in patients, which was defined as the antibiotic with coverage for the known or suspected gram-positive infection selected by the treating physician or site. During the post-period, both components of the critical pathway were implemented by initiating 1,500 mg dalbavancin as a single IV dose over 30 minutes in a new set of patients enrolled based on the same guideline-based criteria used in the pre-period. For both pre- and post-periods, patients were assessed at baseline (date of enrolment), 48 to 72 hours following date of enrolment or discharge, 10 to 14 days following date of enrolment, and 44 to 51 days following date of enrolment.

ADVANCE was conducted to estimate the difference in hospital admission rates at initial care between patients with ABSSSI who received care before (pre-period) and after (post-period) the implementation of the critical pathway. The study design of ADVANCE was similar to ENHANCE with a few differences to note. First, ENHANCE recruited among patients with ABSSSI who were admitted to the ER, while ADVANCE recruited among patients with ABSSSI who presented to the ER. Therefore, patients enrolled in ADVANCE received dalbavancin at the point of care in the ER and were subsequently sent home at the discretion of the treating physician. Finally, patients enrolled in ADVANCE had an additional assessment at 24 hours following enrolment in the post-period, while patients in the pre-period were not assessed at 48 to 72 hours after enrolment.

Efficacy Results

The mean difference between pre- and post-period in the total infection-related length of stay during the entire ENHANCE study was 1.6 days (95% CI, 0.6 to 2.6 days; P = 0.003), in favour of the post-period. The results of the secondary analysis, after adjusting for age and immunocompromised status, were generally consistent with the primary analysis. Analysis including time spent in prolonged (greater than 1 day) observation and in patients who completed the study were generally consistent with the observed difference in the primary analysis with inpatients only for the entire duration of the study.

The ABSSSI-related hospital admission rate at initial care in ADVANCE was 38.5% and 17.6% in the pre- and post-period group, respectively. The difference between pre- and post-period in the ABSSSI-related hospital admission rate at initial care was in favour of the post-period group ($P < 0.001$). The results of the secondary analysis after adjusting for age, race, insurance type, prior resource use, and SIRS score were generally consistent with the primary analysis.

All secondary outcomes were exploratory as the studies were not powered for secondary outcomes and no adjustments for multiple comparisons were made. In ADVANCE, the 12-Item Short Form Survey Mental and Physical Health Component Scores at Day 14 relative to baseline was used to assess HRQOL. The trial found no difference between the 2 assessment groups.

Harms Results

In ENHANCE, a total of 3 (6.2%) and 20 (47.6%) patients in the pre- and post-period groups, respectively, reported at least 1 AE. The most common (reported in more than 5%) AE was pyrexia in 3 patients (7.1%) in the post-period. No patients discontinued study due to any adverse event and no deaths were reported in the study. A total of 1 (2.1%) and 3 (7.1%) patients in the pre- and post-period groups, respectively, reported at least 1 serious adverse event.

In ADVANCE, a total of 22 patients (14.1%) and 68 (44.4%) patients in the pre- and post-period groups, respectively, reported at least 1 AE. The most common (reported in more than 5%) AE was cellulitis in 8 patients (5.2%) and diarrhea in 8 patients (5.2%) in the post-period. No patients discontinued study due to any adverse event and no deaths were reported in the post-period group; 2 deaths were reported in the pre-period group, 1 each due to congestive cardiac failure and road traffic accident. A total of 11 (7.0%) and 16 (10.5%) patients in the pre- and post-period groups, respectively, reported at least 1 SAE; most common SAEs were not reported.

Critical Appraisal

Internal Validity

The interpretation of the efficacy and safety results from both the ENHANCE and ADVANCE studies may be limited due to the pre-post pragmatic (non-randomized and open-label) study design. Each site enrolled patients consecutively into both the pre- and post-period groups and as a result, the study lacked a concurrent control and patients were not randomized to each arm. The study design may have also introduced the risk for time-related confounders such as changes between the pre- and post-period in the local antimicrobial resistance patterns as well as site- and physician-specific approach to usual care for the treatment of ABSSSI. In comparison to the post-period in which site staff were trained on the critical pathway and the post-period protocol, staff were only trained on the pre-period protocol for the pre-period. As a result, it is uncertain how much of the treatment effect observed in the post-period group was due to the efficacy of dalbavancin versus the effectiveness of the entire critical pathway.

Of note, treating physicians were not trained on the protocol (e.g., study objectives, exclusion and inclusion criteria, intervention and comparator treatment, and outcomes of interest) for the pre-period to limit performance bias when selecting usual care for the treatment of ABSSSI. This was particularly important because patients were discharged or sent home from

the ER at the discretion of the treating physician during the pre- and post-periods which may have an impact on the length of hospital stay and admission rate.

The interpretation of the results may be further limited due to the missing data. Since the analyses were conducted using the observed cases approach and a relatively high and unbalanced study withdrawal due to lost to follow-up was reported in 4 patients (8.3%) in the pre-period and 9 patients (20.9%) in the post-period in ENHANCE, the direction of attrition bias is uncertain. The interpretation of the results in ADVANCE may be further limited due to the 104 (68.0%) patients in the post-period group having received concomitant therapy with other antibiotics at initial care, thereby removing the difference in the treatment received between the pre- and post-period.

External Validity

To optimize the selection of patients with ABSSSI that best represented real-world outpatients, both ENHANCE and ADVANCE used minimal inclusion and exclusion criteria. Although this would support generalizability to clinical practice, there may still be potential differences between the study sites and the Canadian practice in the approach to usual care for the treatment of ABSSSI according to guidelines on the management of patients with ABSSSI in the acute care setting and the recommended treatment options or regimens and the local antimicrobial resistance patterns. Further, the generalizability of the results to the Canadian patient population with ABSSSI may be limited given that all patients were sourced from 1 hospital in ENHANCE.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision-tree
Target population	Treatment of adult patients with non-severe and severe ABSSSI
Treatment	Dalbavancin
Submitted price	Dalbavancin, 500 mg, lyophilized powder in vial: $957.1679
Treatment cost	$2,872 per patient
Comparators	• Vancomycin (IV) • Linezolid (IV) • Cefazolin (IV) • Ceftriaxone (IV) • Daptomycin (IV)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	6 months (197 days)
Key data source	Clinical efficacy and safety: DISCOVER 1 trial, DISCOVER 2 trial and sponsor-submitted ITC Hospital discharge rates: clinical expert opinion and published literature
Key limitations	• The assumption of equivalent efficacy between dalbavancin IV and active comparators was associated with a high degree of uncertainty. Based on the CADTH clinical review, the evidence of comparative efficacy from the DISCOVER trials for vancomycin IV, with a possible switch to oral linezolid, was uncertain due a lack of direct or indirect comparative evidence for ceftriaxone IV and cefazolin IV relative to dalbavancin IV, and concerns about generalizability to standard treatment. • There was no direct or indirect comparative evidence to support early discharge rates associated with dalbavancin IV. The sponsor modelled reduced hospitalization rates for patients with non-severe symptoms treated with dalbavancin IV relative to active comparators using the Talan et al. 2020 study, which performed a naive comparison of hospitalization rates before and after dalbavancin IV was administered in a hospital setting. The study design was prone to risk of selection and performance bias. Further, there was a lack of a concurrent comparator, lack of randomization, time-related confounders, missing data, and attrition bias, which may have introduced a bias in the length of hospital stay and admission rate in favour of dalbavancin IV. As such, this assumption was highly uncertain. • There was insufficient evidence to support early discharge rates associated with dalbavancin IV, which was a key driver of the results of cost savings derived in the sponsor's economic evaluation. • The sponsor did not include oral therapies that clinical experts consulted by CADTH deemed relevant in clinical practice in Canada. The cost-effectiveness of dalbavancin IV compared to these omitted comparators is unknown. • The sponsor assumed patients switch to an oral antibiotic after hospital discharged and adopted a higher rate of disease recurrence with oral treatments relative to IV treatments. This increased the subsequent treatment costs for comparators relative to dalbavancin IV. CADTH was unable to validate the sponsor's estimated increase in recurrence rate with the sponsor's reference.
CADTH reanalysis results	• Given the key limitations with the available clinical evidence, the comparative clinical effects of dalbavancin IV compared to active comparators for ABSSSI were highly uncertain. The CADTH reanalysis assumed that there would be no difference in treatment effects (i.e., no difference in total QALYs) and a cost comparison between dalbavancin IV and its comparators was conducted to highlight the differences in drug costs. • The treatment cost of dalbavancin IV ($2,872 per patient) was higher than all active comparators, which range from $97 to $1,775 for IV treatments. • There was insufficient clinical evidence to justify a price premium for dalbavancin IV above all other comparator treatments. The submitted price of dalbavancin IV would need to be reduced by at least 38% to 97% to be equivalent to the lowest priced generic IV treatment.

Budget Impact

CADTH identified several limitations with the sponsor's analysis. The proportion of patients covered by public drug plans, the number of eligible patients and treatment duration was uncertain. Further, the market share of dalbavancin IV may have been underestimated. CADTH did not conduct a base case analysis, as there was a high degree of uncertainty. However, CADTH found the budget impact of dalbavancin IV was highly sensitive to market share of dalbavancin IV and the eligible population size.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: September 28, 2022

Regrets: Four expert CDEC members did not attend

Conflicts of interest: None