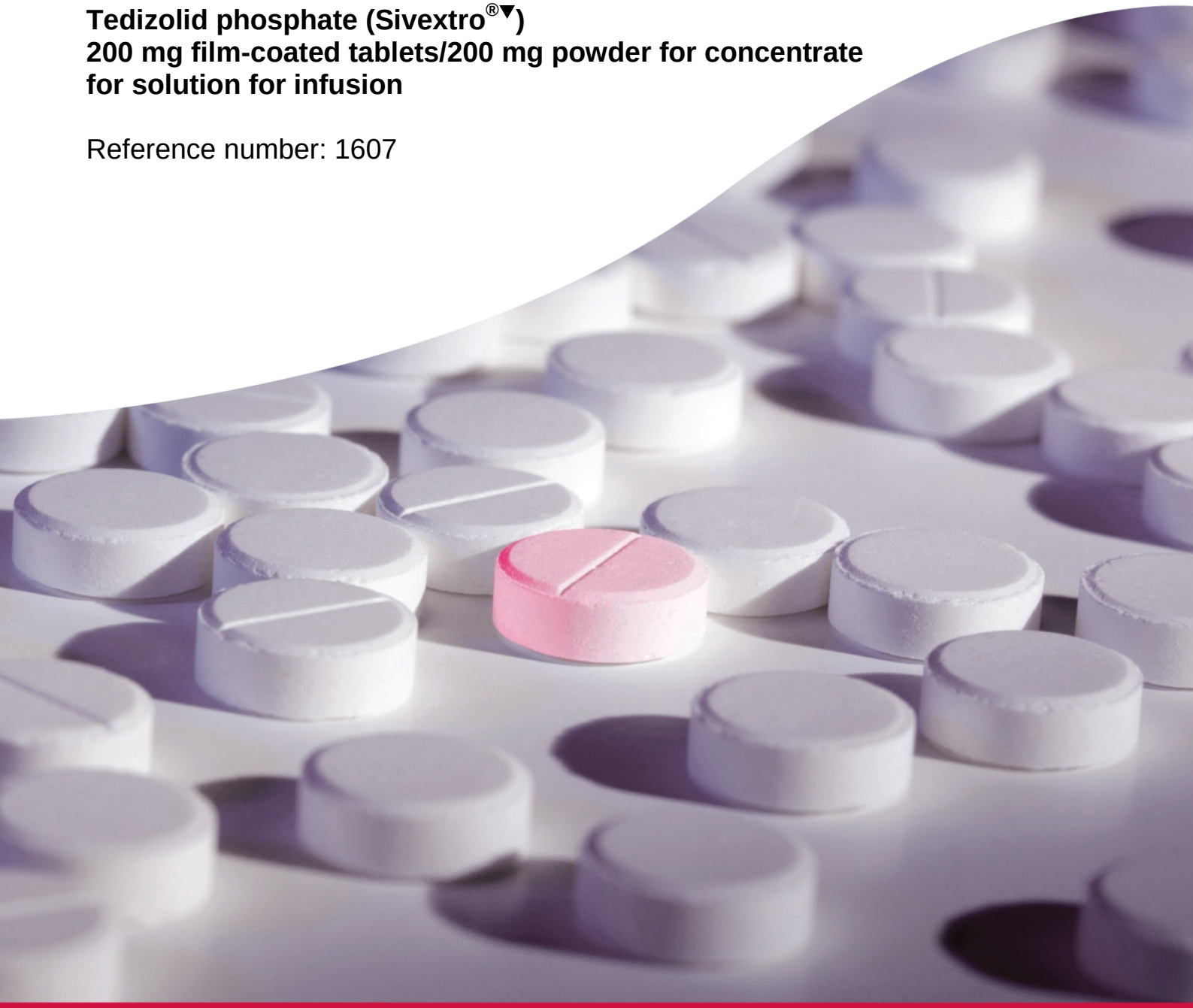
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tedizolid phosphate (Sivextro®▼)
200 mg film-coated tablets/200 mg powder for concentrate for solution for infusion

Reference number: 1607



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AWMSG Secretariat Assessment Report
Tedizolid phosphate (Sivextro®▼) 200 mg film-coated tablets/200 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Merck Sharp & Dohme Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Tedizolid phosphate (Sivextro®▼) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults[2,3].
Dosing	The recommended dosage is 200 mg once daily for six days. Tedizolid phosphate film-coated tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated. Refer to the Summary of Product Characteristics for further dosing information[2,3].
Marketing authorisation date	23 March 2015[4]

2.0 DECISION CONTEXT

2.1 Background

Acute bacterial skin and skin structure infections (ABSSSIs) are frequently caused by Gram-positive bacteria, particularly *Streptococcus pyogenes* and *Staphylococcus aureus* (*S. aureus*), including those caused by methicillin-resistant *S. aureus* (MRSA)[5,6]. *Staphylococcus aureus* accounts for more than 40% of all skin and soft tissue infections (SSTIs), with a significant proportion caused by MRSA[7]. MRSA is a significant cause of antibiotic-resistant healthcare-associated and community acquired infections worldwide[5,7]. New antibacterial medicinal products, especially those available as an oral formulation, are therefore needed to treat infections due to drug-resistant Gram-positive bacteria in both hospital and community settings[5].

In Wales, *S. aureus* bacteraemia is one of the top 10 blood stream infections and has an incidence rate of 21.1 per 100,000[8]; with MRSA bacteraemia accounting for 5 per 100,000 hospital bed days in 2014, although MRSA rates are generally declining year on year in Wales[9]. Current standard practice in NHS Wales is to treat all severe skin and soft tissue infections (SSTIs) associated with MRSA empirically with glycopeptides such as vancomycin initially, using an alternative agent where appropriate[10,11]. Currently, linezolid, an oxazolidinone, is the only licensed medicine allowing an intravenous (IV)-to-oral treatment switch without necessitating a change in the antibiotic and/or dose[2,3].

Tedizolid phosphate is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo to microbiologically active tedizolid[5]. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis[2,3].

The applicant company has requested that the All Wales Medicine Strategy Group (AWMSG) consider tedizolid phosphate for use in a subpopulation of adult patients with ABSSSI caused by MRSA only[1]. In this clinical population, tedizolid phosphate is expected to displace linezolid in a post-vancomycin treatment setting (or where vancomycin is not appropriate) on the specific advice of local microbiologists or specialists in infectious disease[1].

2.2 Comparators

The comparator included in the company submission was linezolid (Zyvox®)[1].

2.3 Guidance and related advice

- All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC). National Prescribing Indicators 2015–2016. Supporting information for prescribers (2015)[12].
- Welsh Analytical Prescribing Support Unit (WAPSU). National Prescribing Indicators. Analysis of antibacterial prescribing data to March 2014 (2014)[13].
- National Institute for Health and Care Excellence (NICE). Quality Standard (QS) 61. Infection prevention and control (2014)[14].
- Welsh Government. Code of practice for the prevention and control of healthcare associated infections (2014)[15,16].
- National Institute for Health and Care Excellence (NICE). Clinical Guideline (CG) 139. Infection: Prevention and control of healthcare-associated infections in primary and community care (2012)[17].
- NICE. Public Health (PH) Guidance 36. Prevention and control of healthcare-associated infections: quality improvement guide (2011)[18].
- Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *S. aureus* (MRSA) infections in the United Kingdom (2009)[11].
- Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Guidelines for the control and prevention of methicillin-resistant *S. aureus* (MRSA) in healthcare facilities (2006)[19].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a Statement of Advice for dalbavancin (Xydalba®)[20].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from two pivotal phase III trials, ESTABLISH-1 and ESTABLISH-2, which were designed to compare the efficacy and safety of tedizolid phosphate with both oral and IV-to-oral linezolid in adult patients with ABSSSI[1]. Due to their identical design these trials will be described together. The company submission also included a subpopulation pooled analysis to determine the efficacy of tedizolid phosphate compared with linezolid in patients with ABSSSI caused by MRSA[1].

3.1 The ESTABLISH trials

ESTABLISH-1 and ESTABLISH-2 were randomised, double-blind, double-dummy, multicentre, multinational, phase III noninferiority trials, which investigated the efficacy and safety of tedizolid phosphate in patients with ABSSSI[1,5,21,22]. The ESTABLISH-1 trial was conducted in the outpatient setting[1]. Patients were eligible for study inclusion if they were ≥ 18 years (ESTABLISH-1) or ≥ 12 years (ESTABLISH-2) of age with an ABSSSI (cellulitis/erysipelas, major cutaneous abscess or wound infection) that had a minimum total lesion surface area of 75 cm^2 and were suspected or documented to be associated with a Gram-positive pathogen[1,5,21,22]. Patients with chronic infection or those with severe or complicated infections were excluded from the studies[1,21,22].

In the ESTABLISH-1 trial, patients (n = 667) were randomised 1:1 to receive either 200 mg of tedizolid phosphate (n = 332) orally once daily for six days or 600 mg of linezolid (n = 335) orally twice daily for 10 days[1,5,22]. In the ESTABLISH-2 trial, patients (n = 666) were randomised 1:1 to receive either IV tedizolid phosphate 200 mg once daily for six days (n=332) or IV linezolid 600 mg twice daily for 10 days (n=334), with an optional oral step-down[1,5,21]. All patients that received at least two or more IV doses could then be switched to oral treatment if they met at least two of the following criteria: no increase in lesion area; temperature < 37.7^{o}C; no worsening of local signs or symptoms of the primary infection site; or improvement of at least one local sign or symptom since previous visit. Baseline characteristics and demographics were similar between the two treatment groups.

In both studies, the primary outcome was the early clinical response at the 48- to 72-hour visit (defined as cessation of spread and absence of fever [ESTABLISH-1] or as ≥ 20% decrease in lesion area [ESTABLISH-2]) in the intent-to-treat (ITT; comprising of all randomised patients; see Glossary for endpoint definition) populations. Patients were defined as responders, non-responders, or indeterminates according to the objective criteria outlined in Appendix 1. Patients assigned an indeterminate response were considered non-responders for the purposes of determining clinical response at the 48- to 72-hour visit. A two-sided 95% confidence interval (CI) for the observed difference in the primary endpoint measure between tedizolid phosphate and linezolid was calculated. Noninferiority was concluded if the lower limit of the 95% CI was –10% or higher. According to this criterion, noninferiority was met in both trials in the ITT population (see Table 1). Results for the secondary endpoints and for each of the sensitivity analyses of the primary endpoint in the ITT population were consistent with those for the primary outcome[1].

Table 1. Primary endpoint results of the ESTABLISH trials[1,21,22]

	Response	ESTABLISH-1			ESTABLISH-2		
		Tedizolid phosphate n (%)	Linezolid n (%)	Difference (95% CI)	Tedizolid phosphate n (%)	Linezolid n (%)	Difference (95% CI)
Primary endpoint (ITT population)							
No increase from baseline at 48- to 72-hour visit in lesion area and length and width, and absence of fever*	N	332	335	–	332	334	–
	Responder	264 (79.5)	266 (79.4)	0.1 (–6.1, 6.2)	285 (85.8)	272 (81.4)	4.4 (–1.2, 10.1)
	Non-responder	27 (8.1)	35 (10.4)		33 (9.9)	45 (13.5)	
	Indeterminate	41 (12.3)	34 (10.1)		14 (4.2)	17 (5.1)	
≥ 20% decrease from baseline in lesion area at the 48- to 72-hour visit†	N	332	335	–	332	334	–
	Responder	259 (78.0)	255 (76.1)	1.9 (–4.5, 8.3)	283 (85.2)	276 (82.6)	2.6 (–3.0, 8.2)
	Non-responder	50 (15.1)	56 (16.7)		44 (13.3)	44 (13.2)	
	Indeterminate	23 (6.9)	24 (7.2)		5 (1.5)	14 (14.2)	

CI: confidence interval; ITT: intent-to-treat; N: number of patients in population; n: number of patients in specific category

* Primary endpoint in the ESTABLISH-1 trial and sensitivity analysis in the ESTABLISH-2 trial
† Primary endpoint in the ESTABLISH-2 trial and sensitivity analysis in the ESTABLISH-1 trial

3.2 Pooled analysis: MRSA sub-population

In the ESTABLISH studies, *S. aureus* represented over 80% of the pathogens within the microbiological intent to treat (MITT) group; with MRSA accounting for 35% of infections. In the ESTABLISH-1 trial, MRSA was prevalent in 42.1% (88/209 patients) and 43.1% (90/209 patients) of cases in the tedizolid phosphate and linezolid treatment groups, respectively. In the ESTABLISH-2 trial, MRSA was prevalent in 26.9% (53/197 patients) and 27.7% (56/202 patients) of cases in the tedizolid phosphate and linezolid treatment groups, respectively[1].

Results from the pooled analysis of the ESTABLISH studies demonstrated that the proportion of patients with ABSSSI caused by MRSA achieving early clinical response (defined as ≥ 20% decrease in lesion area at the 48- to 72-hour visit) was comparable between the tedizolid phosphate and linezolid treatment groups (see Table 2). Results for the secondary endpoints were consistent with those for the primary outcome. However, the pooled analysis of MRSA cases was not powered to assess noninferiority.

The outcomes in the subgroup analyses of the pooled clinical data showed a numerically lower response in the tedizolid group compared with the linezolid groups in patients with a higher body mass index, patients with diabetes and in patients with major cutaneous abscess[5].

Table 2. Primary endpoint results for the pooled analysis (MRSA subpopulation)[1]

	Response	Tedizolid phosphate (N = 141) n (%)	Linezolid (N = 146) n (%)	Difference (95% CI)
Pooled ESTABLISH-1 and ESTABLISH-2 (MITT population)				
≥ 20% decrease from baseline in lesion area at the 48- to 72-hour visit	Responders	114 (80.9)	111 (76.0)	4.9 (–4.8, 14.4)
	Non-responders	16 (11.3)	21 (14.4)	
	Indeterminates	11 (7.8)	14 (9.6)	

CI: confidence interval; MITT: microbiological intent-to-treat; N: number of patients in population; n: number of patients in specific category

3.3 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) considered the safety profile of tedizolid phosphate administered either at a daily dose of 200 mg for six days, by the oral route or IV to be acceptable[5].

The overall incidence of treatment-emergent adverse events (TEAEs) reported in the tedizolid phosphate group was comparable with the linezolid group based on the pooled analysis of safety data from the ESTABLISH trials (42.7% versus 43.2%, respectively)[1,5]. The majority of TEAEs reported were mild or moderate in severity with few leading to discontinuation in either treatment arm (tedizolid phosphate: 0.5%; linezolid: 0.9%). Treatment-related TEAEs were less frequent in the tedizolid phosphate group than in the linezolid group (22.4% versus 27.9%, respectively)[1,5]. The most common treatment-related TEAEs reported in ≥ 2% of patients were nausea, headache and abscess, of which nausea was reported less frequently in the tedizolid phosphate group than in the linezolid group. Overall, fewer patients treated with tedizolid phosphate reported gastrointestinal AEs compared with patients treated with linezolid (16% versus 23%, respectively)[1,5,21,22]. Oxazolidinones, such as tedizolid phosphate and linezolid, inhibit bacterial and human mitochondrial protein synthesis. As a result, the use of these and other antibiotic agents that inhibit protein synthesis

can be associated with AEs such as myelosuppression, peripheral and optic neuropathies, and lactic acidosis. The incidence of substantially abnormal absolute neutrophil count (ANC), haemoglobin values, and platelet counts were roughly similar between the two treatment groups[5]; however fewer patients treated with tedizolid phosphate had substantially abnormal platelet counts (defined as < 75% of the lower limit of normal [LLN] and < 75% of a patient's abnormally low baseline count) compared with patients treated with linezolid (2.1% versus 4.5%)[1,5,21,22]. Prokocimer et al (2013) stated that although low platelet counts were less than half as frequent in the tedizolid group (2.3%) as in the linezolid group (4.9%), the study (ESTABLISH-1) was not powered to make conclusions about the risk of myelosuppression with tedizolid phosphate[22].

3.2 AWTTC critique

- The company suggest tedizolid phosphate should be considered for use in the subpopulation of adult patients with ABSSSI caused by MRSA only[1]. Tedizolid phosphate is primarily active against Gram-positive bacteria. It is bacteriostatic against enterococci, staphylococci, and streptococci in vitro only. Tedizolid phosphate is generally not active against Gram-negative bacteria[1–3]. The company does not wish AWMSG to consider the use of tedizolid phosphate in "mixed infections" (where the infection involves both Gram-positive and Gram-negative organisms). It should be noted that patients with "mixed infections" were included in the ESTABLISH-1 and ESTABLISH-2 trials providing they had a Gram-positive bacterial pathogen known to cause ABSSSI at baseline; it is therefore possible that patients with mixed-infections were also included in the MITT analysis set.
- The majority of patients enrolled in the ESTABLISH trials did not have severe ABSSSI[5], and patients receiving systemic antibiotics with Gram-positive activity within 96-hours before the first dose of tedizolid phosphate or linezolid, or those with previous treatment failure of the same infection site were specifically excluded from these trials[21,22]. The extent to which the trial observed outcomes will be achieved in the specific subgroup of patients who have failed or are otherwise unsuitable for vancomycin treatment in practice is therefore uncertain.
- However, based on the company's response throughout the marketing authorisation application process, CHMP concluded that the data provided were sufficiently supportive of the fact that tedizolid phosphate is also effective in more severe ABSSSI[5].
- No UK or Welsh patients were included in either ESTABLISH-1 or ESTABLISH-2[1]. The company does not believe that the absence of UK or Welsh patients in these studies adversely affects the generalisability of the study data to routine clinical practice in NHS Wales, for the following reasons: the ESTABLISH trials were conducted in a large number of centres in Europe and across the rest of the World; over 80% of patients in each trial gave their ethnicity as white; enrolled patients had a Food and Drug Administration (FDA)-defined ABSSSI at baseline; and there were no meaningful differences between treatment groups[1].
- The definition for the primary endpoint in the ESTABLISH-1 trial was in accordance with the draft FDA guidelines that were current at the time of finalisation of the study protocol. Although the FDA subsequently updated the recommendation resulting in the removal of the temperature component, the protocol for this trial was not changed and the analysis plans were not modified. The company conducted sensitivity analyses to address these changes in regulatory guidance and other recommendations regarding the definitions of the primary and secondary outcome measures as well as to determine the robustness of the primary endpoint[1,23]. The sensitivity analyses were supportive of the primary and secondary analyses[1].

- There were missing data in both of the ESTABLISH trials. The company has not provided any information regarding the missing data in the ESTABLISH-1 trial. In the ESTABLISH-2 trial, missing data did not affect the noninferiority findings: a tipping point analysis showed that if all patients with missing data in the linezolid group were considered to be responders, and all those in the tedizolid phosphate group with missing data non-responders, noninferiority was preserved (95% CI: –6.9 to 3.7)[1,21]. A multiple imputation analysis further confirmed these results (95% CI: –4.7 to 6.3)[1,21].
- The lower dosage and shorter duration treatment course of tedizolid phosphate may result in an improved safety/tolerability profile and compliance with oral treatment[1].
- Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid and the risk of these effects appears to be related to the duration of treatment[24,25]. Consequently, in the event that linezolid is administered in specified groups of patients at higher risk of these effects, close monitoring of haemoglobin levels, blood counts and platelet counts is specifically indicated in the Summary of Product Characteristics (SPC)[25]. The company highlight that there is no such monitoring requirement associated with the marketing authorisation for tedizolid phosphate[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of tedizolid phosphate compared against linezolid following failure or intolerance of vancomycin or where vancomycin is not appropriate in the treatment of suspected or confirmed ABSSSI due only to MRSA in adults[1]. The company has therefore restricted its economic evidence to a specific subgroup of the tedizolid phosphate licence[1–3].

In the model, hospitalised patients with ABSSSI due to MRSA, who have failed, are intolerant, or are unsuitable for vancomycin treatment, may be treated with tedizolid phosphate or linezolid. The company assumes therapeutic equivalence of tedizolid phosphate and linezolid in this restricted population based on subgroup analyses in the 35% of patients with ABSSSI due to MRSA enrolled in the ESTABLISH-1 and ESTABLISH-2 phase III randomised, double-blind, noninferiority trials[21,22] (see Section 3.1). Tedizolid phosphate 200 mg once daily for six days is assumed to be given by IV infusion for two days, followed by oral treatment for four days. Linezolid 600 mg twice daily for 10 days is assumed to be given by IV infusion for two days, followed by oral treatment for eight days[1]. There is assumed to be no difference in length of hospitalisation, but other areas of resource use differ between treatments. Linezolid accrues shorter IV preparation time but greater nurse time for IV administration twice daily compared with once daily for tedizolid phosphate. In addition, routine laboratory monitoring is assumed to occur twice during the 10 days of linezolid treatment, compared with no monitoring for tedizolid phosphate treatment. Health professional time is informed by published expert opinion on use of IV antibiotics in the treatment of ABSSSI in Canada[26], and costed with published UK unit costs. Laboratory monitoring costs are based on Scottish data.

Given the short treatment duration and assumption of equivalent outcomes, discounting to net present value is not required[1].

4.1.2 Results

Results of the CMA are presented in Table 3. Under an assumption of therapeutic equivalence, tedizolid phosphate 200 mg once daily for six days is estimated to be cost saving compared with linezolid 600 mg twice daily for 10 days, at their current list prices. The main driver of the cost savings is the additional monitoring costs assumed for linezolid treatment.

Table 3. CMA results[1].

Item	Tedizolid phosphate	Linezolid	Difference
Medicine acquisition cost	£862.00	£890.00	–£28.00
Administration cost	£66.27	£79.40	–£13.13
Monitoring cost	£0	£50.91	–£50.91
Total cost	**£928.27**	**£1,020.31**	**–£92.03**

The company has provided scenario analyses exploring six days of IV treatment with both agents and up to 14 days of treatment with linezolid as per its SPC recommendation of 10–14 days of treatment[24,25]. Each scenario increases the total costs of linezolid relative to tedizolid phosphate due to additional administration and/or acquisition costs, with results as would be expected. However, it should be noted that the clinical outcomes observed in the trials with linezolid were achieved with only 10 days of treatment[21,22].

4.1.3 AWTTC critique

The company has presented a CMA of tedizolid phosphate 200 mg once daily for six days compared against linezolid 600 mg twice daily for 10 days, specifically in patients with ABSSSI due to MRSA who have failed or are otherwise unsuitable for vancomycin treatment. The company assumes these regimens are therapeutically equivalent based on subgroup analyses in around 35% of patients enrolled in two noninferiority trials, which observed comparable outcomes across several efficacy endpoints but are not powered to determine equivalence statistically. The majority of patients enrolled in the trials did not have severe ABSSSI[5], and patients receiving systemic antibiotics with Gram-positive activity within 96 hours before the first dose of tedizolid phosphate or linezolid, or those with previous treatment failure of the same infection site were specifically excluded from these trials[21,22]. The extent to which the trial observed outcomes will be achieved in the specific subgroup of patients who have failed or are otherwise unsuitable for vancomycin treatment in practice is therefore uncertain. A key driver of the estimated cost savings with tedizolid phosphate is the assumed additional costs of laboratory monitoring for linezolid. However, under an assumption of therapeutic equivalence, at current list prices tedizolid phosphate would be associated with lower costs than linezolid, even if laboratory monitoring costs were not considered.

Key strengths of the economic evidence include:

- Direct comparative trial data support as assumption of comparable efficacy for several outcomes in patients with ABSSSI.

Key limitations and uncertainties in the economic evidence include:

- The company has limited its economic evidence to a subset of the licensed indication for tedizolid phosphate[1–3]. This related to use of tedizolid phosphate only where linezolid would be the appropriate medicine specifically in patients with ABSSSI due to MRSA who have failed or are otherwise unsuitable for

vancomycin treatment. Alternative treatment options in patients with ABSSSI due to MRSA are not considered.

- The CMA framework assumes therapeutic equivalence in all domains of health outcomes. The assumption of therapeutic equivalence is based on subgroup analyses of noninferiority trials, which have limitations:
    - These report comparable outcomes for a range of efficacy endpoints except sustained clinical success at 18–25 days after end of therapy, which favoured linezolid treatment in per protocol analysis (96.4% versus 100%; difference −3.6% [95% CI: –8.9 to –0.2]). However, these subgroup analyses are not powered for assessment of equivalence.
    - The majority of the estimated cost savings arises from differences in administration and monitoring requirements in favour of tedizolid phosphate. Whether or not the assumed costs of monitoring reflect actual additional routine monitoring costs with linezolid in practice is uncertain; however, acquisition costs of a full six-day course of tedizolid phosphate treatment are also lower than those for a full 10-day course of linezolid at current list prices, and tedizolid phosphate would remain cost saving if monitoring costs were excluded from the analysis.
    - The scenario analyses exploring up to 14 days of treatment with linezolid are of limited informative value given that the outcomes underpinning the assumption of therapeutic equivalence were achieved with a maximum of 10 days of linezolid treatment.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost effectiveness analyses of tedizolid phosphate relevant to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on commercial in confidence hospital audit data for the UK, which have been applied to the population of Wales, the company estimates there were [commercial in confidence figure removed] complicated SSTIs (cSSTIs) or ABSSSI in Wales in 2011. This is reported to have been confirmed as a reasonable estimate with Welsh infection specialists. As MRSA bacteraemia rates are reported to be decreasing over time, the company assumes there would be no increase in the number of cases of ABSSSI due to MRSA in each of the next five years. All patients with suspected or confirmed MRSA infections are assumed to receive treatment[1].

Based on the commercial in confidence hospital audit data, [commercial in confidence figures removed] of these patients received linezolid, which is assumed to reflect the number potentially eligible for treatment with tedizolid phosphate instead. Uptake is anticipated to be 5% in year one, rising to 45% in year five. Costs include acquisition, administration and monitoring costs as estimated for the CMA in Section 4.

5.1.2 Results

The company estimates the introduction of tedizolid phosphate would result in net cost savings, which is presented in Table 4.

Table 4. Company estimates of net cost implications associated with use of tedizolid phosphate for the treatment of ABSSSI due to MRSA[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	¶	¶	¶	¶	¶
Uptake (%)	5	15	25	35	45
Treated patients	¶	¶	¶	¶	¶
Net costs					
Medicine acquisition	¶	¶	¶	¶	¶
Administration and monitoring	¶	¶	¶	¶	¶
Overall net cost (– savings)	¶	¶	¶	¶	¶
¶: commercial in confidence figure removed.					

The company provided an alternative scenario of 100% uptake, which is estimated to result in cost savings of around [commercial in confidence figure removed] per year.

5.1.3 AWTTC critique

- The company's budget impact analysis relates to the use of tedizolid phosphate instead of linezolid in a specific subgroup of patients with ABSSSI due to MRSA, as per the CMA in Section 4. In the absence of complete data on the incidence of ABSSSI due to MRSA in Wales, the company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with tedizolid phosphate.
- The company has based its net budget impact estimates on the figures included in its CMA, which incorporate cost savings related to reduced nursing time for IV administration of tedizolid phosphate compared with linezolid; however, these cost savings would not be realised in practice unless there was an accompanying reduction in nurse staffing levels. The potential cost savings are therefore overestimated. However, assuming therapeutic equivalence and based on acquisition costs alone, a full six-day course of tedizolid phosphate would be less costly than a full 10-day course of linezolid at current list prices.

5.2 Comparative unit costs

The company wishes AWMSG to consider tedizolid phosphate for the treatment of ABSSSI due to MRSA only[1]. The current British National Formulary (BNF) notes that a tetracycline or clindamycin alone, or a combination of rifampicin and sodium fusidate can be used for SSTIs caused by MRSA. A glycopeptide (e.g. vancomycin) can be used for severe SSTIs associated with MRSA, and if a glycopeptide is unsuitable, linezolid can be used on expert advice. It further notes that ceftaroline, tigecycline and daptomycin are also licensed for the treatment of cSSTIs involving MRSA[10].

Table 5 provides comparative acquisition costs of such antibiotic regimens and tedizolid phosphate as examples only. The treatment of ABSSSI due to MRSA should follow local antimicrobial prescribing guidelines and microbiologist advice.

Table 5. Examples regimens and acquisition costs of antibiotics for treatment of ABSSSI due to MRSA

Medicine	Example regimen*	Cost per course†
Tedizolid phosphate (Sivextro®▼) 200 mg oral tablets or vial for IV infusion	200 mg once daily for six days	£862
Linezolid (Zyvox®) 600 mg oral tablets or vial for IV infusion	600 mg every 12 hours for 10–14 days	£890 to £1,246
Vancomycin (non-proprietary) 500 mg vial for IV infusion	1–1.5 g every 12 hours for 10–14 days	£250 to £525
Teicoplanin (Targocid®) 200mg or 400mg powder for solution for injection/infusion	400mg 12 hourly for 3 doses then 6mg/kg every 24 hours for 10-14 days	£81 to £109
Tigecycline (Tygacil®) 50 mg vial for IV infusion	100 mg initially, then 50 mg twice daily for 10–14 days	£678 to £937
Daptomycin (Cubicin®) 350 mg or 500 mg vial for IV infusion	6 mg/kg every 24 hours for 10-14 days	£886 to £1,240
Clindamycin (non-proprietary) 300 mg ampoule for IV infusion	600 mg three times a day for 10-14 days	£354 to £496
Ceftaroline fosamil (Zinforo®) 600 mg powder for concentrate for solution for infusion	600 mg every 12 hours for 5–14 days	£375 to £1,050

IV: intravenous; kg: kilograms; mg: milligrams
This table does not imply therapeutic equivalence of medicines or doses.
* See relevant SPCs[2,3,24,25,27,28] and BNF[10] for dosing details.
† Costs based on BNF list prices 23 June 2015, except tedizolid phosphate based on company information and confirmed in Monthly Index of Medical Specialities (MIMS)[29]. Excludes any reconstitution costs and assumes 70 kg adult.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company do not anticipate that tedizolid phosphate (Sivextro®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7 July 2015
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional clinical information

Table 1A. Criteria for responders and non-responders at the 48- to 72-hour visit in the ESTABLISH trials[1,21]

	ESTABLISH-1	ESTABLISH-2
	Definition	Definition
Responders	• Cessation of spread of the primary ABSSSI lesion, compared with baseline (cessation of spread was defined as no increase in lesion surface area [length x width] compared with baseline • Temperature ≤ 37.6°C at the time of visit as well as the next measurement taken with 24 hours of the 48- to 72-hour visit	• ≥ 20% reduction in the area of erythema, oedema, and/or induration (length x width) of the primary ABSSSI lesion compared with baseline at the 48- to 72-hour visit
Non-responders	• Spread of the primary ABSSSI lesion, compared with baseline (spread of the lesion was defined as an increase in lesion surface area [length x width] as compared to baseline • Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections • Death (all-cause mortality) • Temperature > 37.6°C at the 48- to 72-hour visit (assessed by the investigator) or the next measurement taken within 24 hours of the 48- to 72-hour visit	• < 20% reduction in the area of the primary ABSSSI lesion compared with baseline at the 48- to 72-hour visit • Receipt of any systemic concomitant antibiotic therapy within 72 hours after the first infusion study treatment that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections • Death
Indeterminates	• A patient classified as indeterminate had data missing that were necessary to determine a treatment response.	• A patient with an indeterminate clinical response or with another circumstance that precluded a microbiological evaluation
ABSSSI: acute skin and skin structure infections		