

7.02 BEZLOTOXUMAB, Solution concentrate for I.V. infusion 1000 mg in 40 mL, Zinplava[®], Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Authority Required) listing for bezlotoxumab for prevention of *Clostridium difficile* infection (CDI) recurrence in patients aged 18 years or older with confirmed diagnosis of toxin B positive CDI, who are at high risk of CDI recurrence and receiving antibacterial therapy for CDI. This was the third submission for bezlotoxumab for prevention of CDI recurrence (see Previous PBAC considerations below).
- 1.2 As with the previous submissions, the key rationale for the PBS listing of bezlotoxumab was that there is currently no PBS listed treatments for the prevention of recurrent CDI and bezlotoxumab works via a novel mechanism of action. While there are no other drugs listed on the PBS to prevent recurrent CDIs, subsequent lines of antibiotic therapy are available for treatment of recurrent CDIs. In that sense, bezlotoxumab would delay or reduce the need for patients to access subsequent lines of antibiotics for treatment of CDI.
- 1.3 The basis for the resubmission's requested listing was cost-effectiveness of bezlotoxumab plus standard of care (SoC) versus SoC alone (Table 1).

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients aged 18 year or older with a confirmed diagnosis of toxin B positive CDI, receiving oral antibacterial therapy for CDI, and at high risk of CDI recurrence defined by ≥ 2 risk factors (age ≥ 65 , prior CDI in past 6 months, clinically severe CDI, immunocompromised).
Intervention	Bezlotoxumab 1000mg IV single administration. The dose of bezlotoxumab is 10mg/kg as a single dose IV infusion.
Comparator	Standard of care (SoC) antibacterial therapy including but not limited to vancomycin / metronidazole.
Outcomes	Prevention of recurrence of CDI, reduction in hospitalisations due to CDI recurrence and global cure.
Clinical claim	In patients with high risk of CDI recurrence (patients with ≥ 2 of 4 risk factors), bezlotoxumab with SoC antibacterials is more effective than SoC antibacterials at preventing recurrence of CDI infection with a similar safety profile.

Abbreviations: CDI=*clostridium difficile* infection; IV=intravenous; SoC=standard of care

Source: Table 1-3, p8 of the resubmission

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BEZLOTOXUMAB, concentrated vial for infusion, 1000mg/40mL	1	0	published prices \$4,365.00 (public) \$4,412.02 (private) effective price [REDACTED] (public) [REDACTED] (private)	Zinplava, Merck Sharp & Dohme

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Clostridium difficile infection</i>
PBS Indication:	Clostridium dDifficile Infection
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Treatment criteria:	Patients must be receiving antibacterial therapy for <i>Clostridium difficile infection</i> . CD1
Clinical criteria:	Patients must have confirmed toxin B positive <i>Clostridium dDifficile Infection</i> , AND Patient must be at high risk of recurrence, defined as having two or more risk factors for <i>Clostridium dDifficile Infection</i> recurrence.
Prescriber Instructions:	High risk is defined by the presence of two or more of the following factors: aAge 65 years or older, immunocompromised, history of <i>Clostridium difficile</i> infection in the past 6 months; or clinically severe <i>Clostridium difficile</i> infection. <i>The medical practitioner should request sufficient quantity based on the weight of the patient to provide for a dose of 10 mg per kg.</i>
Administrative Advice:	Repeat administration is not permitted within 90 days of the initial episode. <i>Special Pricing Arrangements apply.</i>

the requested effective price (private) assumed a ready prepared dispensing fee of \$7.15; the current dispensing fee (since January 2019) is \$7.29, resulting in an effective price (private) of \$ [REDACTED].

- 2.2 The resubmission proposed a lower effective DPMQ (via special pricing arrangement) for bezlotoxumab of [REDACTED] (public hospitals) (versus a published price of \$4,365). This was an [REDACTED]% price reduction compared to the July 2018 resubmission (and [REDACTED]% lower compared to the November 2017 submission). The Pre-PBAC response stated the sponsor was willing to reduce the effective price of bezlotoxumab from a DPMQ (public hospitals) of [REDACTED] to [REDACTED] (versus a published price of \$4,365). This was a reduction of approximately [REDACTED]% relative to the proposed price in the main body of the resubmission (and [REDACTED]% lower compared to the November 2017 submission).
- 2.3 The resubmission presented a revised requested restriction for bezlotoxumab. Compared to the restriction considered at the July 2018 PBAC meeting, the resubmission requested a narrower definition of patients at ‘high risk’ of CDI

recurrence. Eligible patients must now have ≥ 2 of 4 risk factors compared to ≥ 1 of 5 risk factors in the previous submission, summarised in Table 2.

Table 2: Definition of high risk population for treatment with bezlotoxumab in the current and previous resubmissions

First resubmission (July 2018)	Current resubmission (July 2019)
Defined ≥ 1 of 5 risk factors:	Defined as ≥ 2 of 4 risk factors:
- Age ≥ 65 years	- Age ≥ 65 years
- Immunocompromised ^a	- Immunocompromised ^a
- History of CDI in past 6 months	- History of CDI in past 6 months
- Clinically severe CDI ^b	- Clinically severe CDI ^b
- Hypervirulent strains (027, 078 or 244 ribotypes) [#]	

Abbreviations: CDI=*clostridium difficile* infection.

[#] Note: the first resubmission did not include hypervirulent strain as a risk factor in the modelled population.

Source: constructed during the evaluation.

^a Patients with compromised immunity, including patients receiving immunosuppressive therapy or with an illness associated with immunosuppression.

^b Severe infection defined as a ZAR score of 2 or higher.

2.4 The ESC recalled that the July 2018 resubmission did not include hypervirulent strains of CDI (ribotypes 027, 078 or 244) as a risk factor in the modelled economic evaluation, on the basis that the 027 ribotype has low prevalence in Australia. Hence, the modelled population was based on an ad hoc analysis of patients with ≥ 1 of 4 risk factors. In addition, the ESC recalled that as the number of patients excluded from the ad hoc analysis was small (n= 32; 3% of total high risk population) and the results for the two subgroup populations were similar, this was unlikely to considerably affect clinical conclusions or model results (paragraph 6.27; Bezlotoxumab July 2018 Public Summary Document (PSD)). However, as outlined in paragraph 2.5 below the ESC considered that the utility of the hypervirulent strains of CDI to predict recurrence is lost by exclusion of this risk factor.

2.5 The evidence supporting the nomination of each of the individual risk factors was unchanged from the previous resubmission. However, the new definition of high risk (for the purposes of restricting access to treatment on the PBS) was poorly justified and potentially inappropriate for several reasons:

- The resubmission did not provide any clinical, pharmacological, biological or other rationale for restricting access to patients with ≥ 2 of 4 risk factors compared to ≥ 1 of 5 risk factors in the previous submissions. Expert advice presented in the current and previous submissions supported use of bezlotoxumab in patients with ≥ 1 of 5 risk factors.
- The resubmission did not demonstrate that the treatment effect for patients with ≥ 2 of 4 risk factors was significantly different to patients with ≥ 1 of 5 risk factors. There was no evidence that the numerically marginally higher treatment effect of CDI recurrence for patients with ≥ 2 of 4 risk factors was beyond that expected by

chance. The modelled economic evaluation was very sensitive to the assumed rates of CDI recurrence.

- The resubmission did not adequately justify excluding hypervirulent strains of CDI as a risk factor. The resubmission argued that this was not a risk factor relevant to the Australian population due to the low prevalence. However, low prevalence in Australia does not reduce the level of risk of recurrence for individuals infected with hypervirulent strains. Ribotype 244 is reasonably common in Australia (paragraph 6.27; Bezlotoxumab July 2018 PSD).
- 2.6 The Pre-Sub-Committee Response (PSCR) acknowledged that the PBAC previously considered the claim of superior comparative effectiveness in patients with ≥ 1 risk factor was reasonable. The PSCR stated that despite this, the PBAC's economic and budgetary concerns remained. The PSCR therefore argued that respecifying the patient population to target a higher risk cohort, who would derive the greatest benefit, was a reasonable approach to address the PBAC's concerns collectively. The ESC agreed with the evaluation that the new definition of high risk was poorly justified biologically and clinically.
- 2.7 The ESC noted that clinically severe CDI is one of the four risk factors listed in the proposed PBS restriction. Severe CDI was defined in the MODIFY I and MODIFY II trials as a ZAR score¹ of 2 or higher at the time of randomisation. The ESC considered that the definition of severe CDI, as per the MODIFY I and MODIFY II trials, should be included in the PBS restriction.
- 2.8 The revised restriction continued to permit patients to undergo repeat administration of bezlotoxumab 90 days after the initial episode. The PBAC had previously considered it was probably and likely appropriate that bezlotoxumab be used more than once within a patient's lifetime, but in the absence of evidence also considered it may be more appropriate to limit use to one dose per lifetime in the restriction (paragraph 2.3, Bezlotoxumab July 2018 PSD). The resubmission did not present any new clinical or economic evidence to support repeat dosing with bezlotoxumab, but stated the Sponsor was willing to enter a risk sharing arrangement (see Financial Management – Risk Sharing Arrangements below).
- 2.9 The revised restriction did not limit the number of bezlotoxumab vials per patient per course; however, the resubmission presented a note at the bottom of the restriction which stated: "As an Authority Required medication physicians will be required to provide the weight of the patient. For patients >100 kg, 2 vials will need to be requested and authorised for dispensing." In the July 2018 resubmission, this was

¹ The Zar score ranges from 1 to 8 and is based on the following factors: age greater than 60 years (1 point), body temperature higher than 38.3°C (100°F) (1 point), albumin level lower than 2.5 g per decilitre (1 point), peripheral white-cell count higher than 15,000 per cubic millimetre within 48 hours (1 point), endoscopic evidence of pseudomembranous colitis (2 points), and treatment in an intensive care unit (2 points).

estimated to impact 7.3% of patients treated for CDI, based on the proportion of patients with ≥ 1 of 5 risk factors in the MODIFY trials. The current resubmission assumed no eligible patients weigh >100 kg and therefore none require 2 vials. This assumption was not supported by the evidence presented in the resubmission. In the MODIFY trials, 4.4% of patients with ≥ 2 of 4 risk factors weighed >100 kg. The model and financial estimates were sensitive to the proportion of patients weighing >100 kg. The PSCR indicated that the proposed risk sharing arrangement would also account for any need for a second vial in patients who weighed >100 kg.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 The TGA approved bezlotoxumab on 8 November 2017 for prevention of recurrence of CDI in adult patients at high risk of recurrence who are receiving antibiotic therapy for CDI. The TGA indication does not define 'high risk' of CDI recurrence. The Advisory Committee on Medicine (ACM) noted that there was not a clear definition of high risk patients, nor did the clinical trials specifically select for high risk patients. However, the ACM noted a high proportion of participants in trials were elderly patients, those who are immunocompromised, had recurrent CDI, and/or infection with hypervirulent strains, and bezlotoxumab was effective in all clinically relevant patient subgroups.
- 3.2 On 8 August 2018, the TGA revised the wording of the indication (the word "antibiotic" was replaced with "antibacterial") and now reads as follows: "ZINPLAVA (bezlotoxumab) is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adult patients 18 years or older at high risk of recurrence of CDI who are receiving antibacterial therapy for CDI. ZINPLAVA is not indicated for the treatment of CDI. ZINPLAVA is not an antibacterial drug. ZINPLAVA should only be used in conjunction with antibacterial drug treatment of CDI."

Previous PBAC considerations

- 3.3 The PBAC rejected the previous submissions (November 2017 and July 2018) on the basis of modest clinical benefit, uncertain and unfavourable cost-effectiveness, and considerably high opportunity cost. In July 2018, the PBAC noted that although statistically significant, the reduction in risk of CDI recurrence was modest for patients with ≥ 1 of 5 risk factors. The economic model was highly sensitive to changes in baseline and recurrent CDI mortality rates and the clinical trials did not demonstrate a mortality benefit of bezlotoxumab compared to placebo.
- 3.4 The resubmission argued that clinical data presented for patients with ≥ 2 of 4 risk factors showed an increase in the magnitude of benefit compared to previous submissions, and a revised economic model demonstrated bezlotoxumab was cost-effective in that subgroup. The clinical significance of the numerically marginally

higher efficacy was unclear for several reasons (see Clinical claim), and the base case ICER remained highly uncertain given the CDI recurrence rates assumed (see Economic analysis). The resubmission did not address any of the PBAC concerns regarding the financial estimates (see Estimated PBS usage & financial estimates).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 CDI recurrence can be due to persistent or newly-acquired *C. difficile* spores. Outgrowth (leading to new toxin expression) is facilitated by gut flora disturbance caused by antibiotics. Patients are at a higher risk of recurrence if they are: age 65 years or greater, immunocompromised, have a history of CDIs, were infected with a hypervirulent CDI ribotype or had a severe episode.
- 4.2 Bezlotoxumab is a human monoclonal antibody that binds with high affinity to *C. difficile* toxin B and neutralises its activity by preventing it from binding to host cells. Bezlotoxumab is thought to prevent CDI recurrence by providing enhanced passive immunity against toxin produced by the outgrowth of persistent or newly-acquired CDI spores. Bezlotoxumab is effective against toxins from a broad range of clinical isolates of CDI. However, bezlotoxumab does not enhance the efficacy of antibiotics used to treat CDI and only prevents recurrence of CDI once patients are cured from their current episode.
- 4.3 The clinical management algorithm was unchanged from the July 2018 resubmission, indicating that patients at 'high risk' of CDI recurrence will be administered bezlotoxumab as add-on to antibiotic for both initial and recurrent CDIs (non-severe and severe episodes). However, the clinical management algorithm does not define high risk of CDI recurrence.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated placebo (or SoC) as the main comparator, unchanged from the previous submissions. In July 2018, the PBAC considered placebo or SoC was the appropriate comparator, but also noted that other options, such as fidaxomicin or faecal microbiota transplantation may be treatments that are avoided or delayed as a result of treatment with bezlotoxumab treatment (paragraph 5.1; Bezlotoxumab July 2018). The PBAC considered that the comparator nominated in the resubmission was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The resubmission was based on the same trials as the previous submissions: two head-to-head randomised trials comparing bezlotoxumab to placebo (MODIFY I and MODIFY II). The resubmission presented new data for a post-hoc subgroup of patients with ≥ 2 of 4 risk factors (age ≥ 65 , immunocompromised, history of CDI in past 6 months, severe CDI, Table 3). Approximately 20% of patients enrolled in the MODIFY trials had ≥ 2 of 4 risk factors, compared to 76% with ≥ 1 of 5 risk factors considered in the July 2018 resubmission. The ESC considered that the use of the post-hoc subgroup of patients with ≥ 2 of 4 risk factors reduced the sample size significantly and increased the potential for selection bias.
- 6.4 The dose of bezlotoxumab administered in the trials was 10mg/kg as a single infusion. Bezlotoxumab was administered alongside SoC oral antibiotics. Antibiotic therapy (metronidazole (1.2-1.5g/day), vancomycin (125-500mg every 6 hours) or fidaxomicin (200mg daily)) was selected by the patient's treating physician and was administered for 10-14 days. Approximately 39%, 56% and 6% of patients with ≥ 2 of 4 risk factors in the bezlotoxumab arm of the trials received therapy with metronidazole, vancomycin and fidaxomicin respectively. Patients taking oral vancomycin or fidaxomicin were also able to take IV metronidazole (1500mg/day).
- 6.5 The predefined trial outcomes included CDI recurrence (primary outcome) and global cure (secondary outcome). In contrast to recurrence, global cure required patients to first obtain clinical cure of the baseline episode AND have no CDI recurrence. Clinical cure was an exploratory outcome in the trials and was defined as: achieving resolution of diarrhoea within 14 days of treatment with SoC antibiotics. In its consideration of the November 2017 submission, the PBAC noted and agreed with the FDA who considered global cure to be a more relevant endpoint as it is 'more interpretable', since clinically, the goal would be to get cured, stay alive, and remain free of recurrent infection over time (paragraph 6.8; Bezlotoxumab November 2017 PSD).

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
MODIFY I	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to <i>Clostridium difficile</i> toxin A), MK-6072 (Human Monoclonal Antibody to <i>C. difficile</i> toxin B), and MK-3415A (Human Monoclonal Antibodies to <i>C. difficile</i> toxin A and toxin B) in Patient Receiving Antibiotic Therapy for <i>C. difficile</i> Infection (MODIFY I).	October 2015
MODIFY II	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to <i>Clostridium difficile</i> toxin B), and MK3415A (Human Monoclonal Antibodies to <i>Clostridium difficile</i> toxin A and B) in Patients Receiving Antibiotic Therapy for <i>Clostridium difficile</i> Infection (MODIFY II)	November 2015
Pooled MODIFY I/II	Wilcox MH, Gerding DN, Paxton IR et al. Bezlotoxumab for Prevention of Recurrent <i>Clostridium difficile</i> Infection.	New England Journal of Medicine 2017; 376(4): 305-317.
	Gerding DN, Kelly CP, Rahav G et al. Bezlotoxumab for prevention of recurrent <i>clostridium difficile</i> infection in patients at increased risk for recurrence.	Clinical Infectious Diseases 2018; 67(5); 649-656.
	Health Technology Assessment (HTA) Report Supportive Analyses High Risk Factors of CDI Recurrence with Confirmed Toxin B Positive CDI.	January 2019.

Note: only main trial citations have been included in this table.
 Shaded areas indicate data previously seen by the PBAC.
 Source: p34 of the resubmission.

Comparative effectiveness

6.6 Main efficacy outcomes for the MODIFY trials are summarised in Table 4, by patient subgroups requested for listing in the current and previous submissions. The main outcome relied on by the resubmission for its clinical claim was CDI recurrence, and the minimal clinically important difference (MCID) was defined as a reduction in recurrence of 8-9%, unchanged from the previous submissions.

Table 4: CDI Recurrence and Global cure rates at 12 weeks (MODIFY I and MODIFY II integrated)

Population	Bezlotoxumab n/N (%)	Placebo n/N (%)	Risk difference % (95% CI) ^a	Relative Risk (95% CI)
CDI recurrence at 12 weeks				
November 2017 submission:				
- All patients	129/781 (16.5)	206/773 (26.6)	-10.0 (-14.0, -6.0)^a	0.62 (0.51, 0.75)
July 2018 resubmission (clinical):				
- ≥1 of 5 risk factors ^b	100/592 (16.9)	174/583 (29.8)	-12.8 (-17.6, -8.0)	0.57 (0.46, 0.71)
- Complement (no risk factor)	29/189 (15.3)	32/190 (16.8)	-1.5 (-9.0, 6.0)	0.91 (0.58, 1.44)
July 2018 resubmission (model):				
- ≥1 of 4 risk factors ^d	97/581 (16.7)	167/562 (29.7)	-13.0 (-17.9, -8.2)	0.56 (0.45, 0.70)
- Complement (no risk factor)	NR	NR	NR	NR
July 2019 resubmission:				
- ≥2 of 4 risk factors ^e	24/146 (16.4)	51/150 (34.0)	-16.8 (-26.7, -6.9)^f	0.48 (0.32, 0.74)[#]
- Complement (<2 risk factors) ^h	31/236 (13.1)	56/241 (23.2)	-10.2 (-17.2, -3.3)	0.57 (0.38, 0.84)^g
- 1 risk factor ^h	20/151 (13.2)	40/154 (26.0)	-12.5 (-21.4, -3.5)	0.51 (0.31, 0.83)^g
- No risk factors ^h	11/85 (12.9)	16/87 (18.4)	-5.2 (-16.8, 6.3)	0.70 (0.35, 1.43) ^g
CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks				
November 2017 submission:				
- All patients	129/625 (20.6)	206/621 (33.2)	-12.2 (-17.1, -7.4)^a	0.62 (0.51, 0.75)
July 2018 resubmission:				
- ≥1 of 5 risk factors ^b	100/471 (21.2)	174/468 (37.2)	-15.9 (-21.6, -10.2)	0.57 (0.46, 0.70)
- Complement (no risk factors*)	29/154 (18.8)	32/153 (20.9)	-2.1 (-11.1, 6.9)	0.90 (0.58, 1.41)
July 2019 resubmission:				
- ≥2 of 4 risk factors ^e	24/113 (21.2)	51/122 (41.8)	-19.2 (-30.8, -7.2)^f	0.51 (0.34, 0.77)[#]
- Complement (<2 risk factors) ^h	31/199 (15.6)	56/202 (27.7)	-11.2 (-19.3, -3.2)	0.56 (0.38, 0.83)^g
- 1 risk factor ^h	20/128 (15.6)	40/127 (31.5)	-14.7 (-25.1, -4.3)	0.50 (0.31, 0.80)^g
- No risk factors ^h	11/71 (15.5)	16/75 (21.3)	-4.8 (-17.9, 8.3)	0.73 (0.36, 1.46) ^g
Global cure at 12 weeks (clinical cure of initial episode and no CDI recurrence)				
November 2017 submission:				
- All patients	496/781 (63.5)	415/773 (53.7)	9.7 (4.8, 14.5)^a	1.18 (1.09, 1.29)
July 2018 resubmission:				
- ≥1 of 5 risk factors ^b	371/592 (62.7)	294/583 (50.4)	12.1 (6.4, 17.7)	1.24 (1.12, 1.37)
- Complement (no risk factors)	125/189 (66.1)	121/190 (63.7)	2.8(-6.9, 17.7)	1.04 (0.9, 1.21)
July 2019 resubmission:				
- ≥2 of 4 risk factors ^e	89/146 (61.0)	71/150 (47.3)	12.6 (1.1, 23.9)^f	1.29 (1.04, 1.59)[#]
- Complement (<2 risk factors) ^h	168/236 (71.2)	146/241 (60.6)	10.5 (1.9, 18.8)	1.18 (1.03, 1.34)^g
- 1 risk factor ^h	108/151 (71.5)	87/154 (56.5)	14.7 (3.9, 25.2)	1.27 (1.07, 1.50)^g
- No risk factors ^h	60/85 (70.6)	59/87 (67.8)	3.4 (-11.0, 17.5)	1.04 (0.85, 1.27) ^g

Shaded areas indicate data previously seen by the PBAC. Text in bold indicate statistical significance.

^a Adjusted for stratification factors of hospitalisation status and SoC therapy.

[#] Not adjusted for stratification factors; estimated during the evaluation using StatsDirect.

* from Gerding et al 2018, breakdown only available for the outcome of CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks.

^a Based on the Miettinen and Nurminen method without stratification unless otherwise stated

^b Including: Age ≥ 65 years, ≥ 1 CDI episode in past 6 months, Immunocompromised, Severe CDI; Zar score ≥ 2 , 027, 078 or 244 strain

^c based on the publication Gerding et al 2018, Figure 2.

^d Including: Age ≥ 65 years, ≥ 1 CDI episode in past 6 months, Immunocompromised, Severe CDI; Zar score ≥ 2 . Although hypervirulent strains was a risk factor for CDI recurrence in the MODIFY trials, it was not included as a risk factor to define patients at high risk of recurrence in the economic evaluation.

^e Including: Age ≥ 65 years, ≥ 1 CDI episode in past 6 months, Immunocompromised, Severe CDI; Zar score ≥ 2 .

^f Based on the Miettinen and Nurminen method stratified by protocol (MODIFY I vs MODIFY II) and SoC therapy.

^g Not adjusted for stratification factors; estimated during the PSCR using MedCalc.

^h Data provided in the PSCR

Source: Tables 2-38 to 2-40, pp85-86- of the resubmission; and constructed during the evaluation.

- 6.7 There were fewer CDI recurrences at Week 12 in patients treated with bezlotoxumab versus placebo for all trial patients (November 2017 submission), patients with ≥ 1 of 5 risk factors (July 2018 resubmission) and patients with ≥ 2 of 4 risk factors (current resubmission). The observed difference was numerically larger for patients with ≥ 2 of 4 risk factors (RD: -16.8% (95%CI: -26.7, -6.9)), compared to patients with ≥ 1 of 5 risk factors (RD: -12.8% (95%CI: -17.6, -8.0)) and the overall population (RD: -10.0% (95%CI: -14.0, -6.0)).
- 6.8 The estimated treatment effect for CDI recurrence at Week 12 in patients with ≥ 2 of 4 risk factors did not meet the nominated MCID (i.e. the upper 95%CI was smaller than -8%). Although the difference was numerically higher for the patients with ≥ 2 of 4 risk factors, the sample size was much smaller and confidence intervals were much wider than the other populations. The PSCR noted that while the analysis of the post-hoc subgroup of patients with ≥ 2 of 4 risk factors was not powered to demonstrate a difference in CDI recurrence between patients with ≥ 1 or ≥ 2 risk factors, it indicated an increase in the magnitude of the benefit in the respecified high-risk population, relative to the risk reduction reported in patients with ≥ 1 risk factors. The PSCR argued that this provided an evidence-based rationale to further restrict the patient population. The ESC noted the numerically larger observed difference for patients with ≥ 2 of 4 risk factors compared to patients with ≥ 1 of 5 risk factors and the overall population. However, the ESC did not consider that this was an adequate basis for further restricting the patient population as the risk of CDI recurrence at 12 weeks was not significantly different across the patient populations. The ESC considered that the use of the post-hoc subgroup introduced the potential for selection bias and hence increased concerns as to whether the observed differences between the patient populations were beyond that expected by chance.
- 6.9 The observed difference between bezlotoxumab and placebo for CDI recurrence was also numerically larger for patients with ≥ 2 of 4 risk factors compared to ≥ 1 of 5 risk factors when considering patients who attained clinical cure of the initial episode. However, the proportion of patients who achieved global cure was similar in patients with ≥ 2 of 4 risk factors (RD: 12.6% (95%CI: 1.1%, 23.9%)) and ≥ 1 of 5 risk factors (12.1% (95%CI: 6.4%, 17.7%)).

- 6.10 Inappropriately, the resubmission did not present results for the complement of patients with ≥ 2 of 4 risk factors (i.e. those with < 2 of 4 risk factors), and did not demonstrate that the treatment effect for patients with ≥ 2 of 4 risk factors was significantly different to patients with ≥ 1 of 5 risk factors requested in the July 2018 resubmission. The PSCR provided data for the complement of patients with ≥ 2 of 4 risk factors (see Table 4 above). The ESC noted that patients with < 2 of 4 risk factors had lower point estimates of relative effect with wide confidence intervals crossing those seen in participants with ≥ 2 of 4 risk factors. However, the ESC noted apparent inconsistencies as the numbers of the complementary subgroups did not add up to the total population (773 total patients in the ≥ 2 of 4 risk factors and complementary subgroups; versus 1,554 total patients in the ITT population).
- 6.11 The ESC considered that CDI recurrence rates for patients with 1 of 4 risk factors may be informative. The ESC noted that bezlotoxumab is effective for patients with 1 or 4 risk factors (RR=0.60, 95% CI 0.46 to 0.77), as presented in Table 5. The ESC noted that patients with 1 of 4 risk factors comprise over 50% of the total patient population and considered that it may not be reasonable to exclude patients with 1 of 4 risk factors as proposed in the resubmission.

Table 5: CDI recurrence rates at 12 weeks (MODIFY I and MODIFY II integrated) by key subgroups

	N		Recurrence, n		Pr (recurrence)		Relative Risk (95% CI)
	Bezlo	SoC	Bezlo	SoC	Bezlo	SoC	
All patients	781	773	129	206	0.17	0.27	0.62 (0.51, 0.75)
≥ 1 of 4 risk factors	581	562	97	167	0.17	0.30	0.56 (0.45, 0.70)
≥ 2 of 4 risk factors	146	150	24	51	0.16	0.34	0.48 (0.32, 0.74)
1 of 4 risk factors	435	412	73	116	0.17	0.28	0.60 (0.46, 0.77)

Bezlo = bezlotoxumab, SoC = standard of care, Pr = Probability

Source: Table 2-38 p85 of the resubmission, Table 4 July 2018 PBAC Meeting Minutes and constructed during the preparation of the ESC Advice.

- 6.12 Table 6 summarises MODIFY trial outcomes by risk factors, presented in the previous submissions. The PBAC previously considered that there was little evidence that the variation in absolute risk difference observed across the patient subgroups were beyond that expected by chance (paragraph 6.12; Bezlotoxumab July 2018 PSD).

Table 6: CDI Recurrence and Global cure rates at 12 weeks by individual risk factor (MODIFY I and MODIFY II integrated)

Population	Bezlotoxumab n/N (%)	Placebo n/N (%)	Risk difference % (95% CI) ^a	Relative Risk (95% CI)
CDI recurrence at 12 weeks, stratified by risk factors				
- Age ≥65 years	60/390 (15.4)	127/405 (31.4)	-16.0 (-21.7, -10.2)	0.49 (0.37, 0.64)
- ≥1 CDI episode in past 6 months	54/216 (25.0)	90/219 (41.1)	-16.1 (-24.7, -7.3)	0.61 (0.46, 0.80)
- Immunocompromised	26/169 (15.4)	41/145 (28.3)	-12.9 (-22.1, -3.8)	0.54 (0.35, 0.84)
- Severe CDI; Zar score ≥2	13/122 (10.7)	28/125 (22.4)	-11.7 (-21.1, -2.5)	0.48 (0.26, 0.86)
- 027, 078 or 244 strain	22/102 (21.6)	37/115 (32.2)	-10.6 (-22.1, 1.3)	0.67 (0.42, 1.05)
- 0 of 5 risk factors	29/189 (15.3)	32/190 (16.8)	-1.5 (-9.0, 6.0)	0.91 (0.58, 1.44)
CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks, stratified by risk factors				
- Age ≥65 years	60/311 (19.3)	127/322 (39.4)	-20.1 (-27.0, -13.2)	0.49 (0.37, 0.63)
- ≥1 CDI episode in past 6 months	54/171 (31.6)	90/182 (49.5)	-17.9 (-27.7, -7.6)	0.64 (0.49, 0.83)
- Immunocompromised	26/137 (19.0)	41/114 (36.0)	-17.0 (-28.0, -6.0)	0.53 (0.35, 0.80)
- Severe CDI; Zar score ≥2	13/82 (15.9)	28/89 (31.5)	-15.6 (-28.0, -2.8)	0.50 (0.28, 0.89)
- 027, 078 or 244 strain	22/78 (28.2)	37/90 (41.1)	-12.9 (-26.8, 1.6)	0.69 (0.44, 1.05)
- 0 of 5 risk factors*	29/154 (18.8)	32/153 (20.9)	-2.1 (-11.1, 6.9)	0.90 (0.58, 1.41)
- 1 of 5 risk factors*	40/234 (17.1)	70/224 (31.3)	-14.2 (-21.9, -6.4)	0.55 (0.39, 0.77)
- 2 of 5 risk factors*	46/171 (26.9)	69/168 (41.1)	-14.2 (-24.0, -4.1)	0.65 (0.48, 0.89)
- ≥3 of 5 risk factors*	14/66 (21.2)	35/76 (46.1)	-24.8 (-39.1, -9.3)	0.46 (0.27, 0.76)
Global cure at 12 weeks (clinical cure of initial episode and no CDI recurrence), stratified by risk factors				
- Age ≥65 years	251/390 (64.4)	195/405 (48.1)	16.2 (9.3, 22.9)	1.34 (1.18, 1.52)
- ≥1 CDI episode in past 6 months	117/216 (54.2)	92/219 (42.0)	12.2 (2.8, 21.3)	1.29 (1.06, 1.58)
- Immunocompromised	111/169 (65.7)	73/145 (50.3)	15.3 (4.4, 26.0)	1.30 (1.08, 1.60)
- Severe CDI; Zar score ≥2	69/122 (56.6)	61/125 (48.8)	7.8 (-4.7, 20.0)	1.16 (0.91, 1.47)
- 027, 078 or 244 strain	56/102 (54.9)	53/115 (46.1)	8.8 (-4.5, 21.8)	1.19 (0.91, 1.56)
- 0 of 5 risk factors	125/189 (66.1)	121/190 (63.7)	2.8(-6.9, 17.7)	1.04 (0.9, 1.21)

Shaded areas indicate data previously seen by the PBAC. Text in bold indicate statistical significance.

^a Based on the Miettinen and Nurminen method without stratification unless otherwise stated

* from Gerding et al 2018, breakdown only available for the outcome of CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks

Source: constructed during the evaluation

6.13 Based on available data, the results indicated that the treatment effect for CDI recurrence given clinical cure was similar for patients with 1 of 5 risk factors (RD: -14.2%, 95%CI: -21.9, -6.4) and 2 of 5 risk factors (RD: -14.2%, 95%CI: -24.0, -4.1). However, there was a prognostic difference across the subgroups given recurrence rates were higher on placebo for patients with 2 of 5 risk factors (41.1%) compared to 1 of 5 risk factors (31.3%). For patients with 0 of 5 risk factors (the complement population in the July 2018 resubmission), there was no difference between

bezlotoxumab and placebo for any of the key trial outcomes.

- 6.14 The PBAC reviewed the CDI recurrence rates in the placebo arm of the MODIFY I and MODIFY II trials to assess the prognostic value of each of the proposed risk factors. The PBAC noted the increased risk of recurrence in those aged ≥ 65 years (recurrence in 33% versus 22% in those < 65 years of age in MODIFY I, 30% versus 21% in MODIFY II) and in those with a history of CDI in the past 6 months (39% versus 23% in MODIFY I, 43% versus 18% in MODIFY II).² The PBAC noted that the data did not support an increase in the risk of recurrence for immunocompromised patients (28% versus 27% in MODIFY I, 28% versus 25% in MODIFY II) or for those with clinically severe CDI (25% versus 28% in MODIFY I, 20% versus 27% in MODIFY II).² For infection with the 027 ribotype there was an increased risk of recurrence although the increase was smaller than that for older age and recent history of CDI (36% versus 30% in MODIFY I, 33% versus 28% in MODIFY II).² Overall, the PBAC considered the proposed risk factors for identifying the population to be treated were not adequately justified.
- 6.15 The PBAC reviewed the bezlotoxumab efficacy (CDI recurrence) results for the subgroups based on the proposed risk factors. Although tests for interaction were not available, the PBAC noted that the treatment effect did not appear to be modified by compromised immunity, clinically severe CDI or strain. Bezlotoxumab did however appear to be less effective in patients aged < 65 years compared with those ≥ 65 (in both MODIFY I and MODIFY II), and possibly in those without a history of CDI in the past 6 months (in MODIFY II). Overall, the PBAC considered the treatment effect of bezlotoxumab was relatively constant (around a 10% reduction in CDI recurrence) for the different patient populations, with the exception of reduced effect in those aged < 65 years.
- 6.16 The PBAC recalled that there was no evidence of a reduction in mortality associated with bezlotoxumab based on the results of the MODIFY trials (paragraph 7.4, Bezlotoxumab July 2018 PSD).

Comparative harms

- 6.17 The resubmission presented a summary of adverse events (AEs) for patients with ≥ 2 of 4 risk factors in the MODIFY trials, which showed similar rates of AEs to the overall population. The findings were similar for patients with ≥ 1 of 5 risk factors, presented in the pre-PBAC response to the July 2018 resubmission.
- 6.18 Overall, there were no statistically significant differences in the proportion of patients with any AEs, drug related AEs, serious AEs or mortality between bezlotoxumab and placebo treatment groups. Approximately 10% of bezlotoxumab patients in the overall

² Table 11-1, pg 6. Clinical Study Report P001, Table 11-1, pg4. Clinical Study Report P002.

trial population reported infusion specific AEs, including nausea (3%), headache (2%), dizziness (1%), fatigue (1%) and pyrexia (1%).

- 6.19 The resubmission presented safety outcomes for the subset of patients with congestive heart failure (CHF) at baseline, summarised in Table 7. The PBAC had previously noted that there was a higher incidence of heart failure in bezlotoxumab treated patients compared to placebo, and amongst those with a history of heart failure, there was a higher incidence of acute heart failure and of mortality in participants treated with bezlotoxumab than those treated with placebo (paragraph 7.3, July 2018 Bezlotoxumab PSD).

Table 7: Summary of adverse events in the subgroup of patients with a history of congestive heart failure (CHF) at baseline in MODIFY I and MODIFY II

Adverse events (AE)	Bezlotoxumab N=118, n(%)	Placebo N=104, n(%)	Risk Difference (95% CI) ^b	Relative risk (95% CI) ^b
At Week 4				
One or more AE	85 (72.0%)	67 (64.4%)	8% (-5%, 20%)	1.12 (0.93, 1.34)
Drug-related AE	9 (7.6%)	5 (4.8%)	3% (-3%, 9%)	1.59 (0.55, 4.58)
Serious AE	43 (36.4%)	35 (33.7%)	3% (-10%, 15%)	1.08 (0.76, 1.55)
Cardiac SAE	11 (9.3%)	6 (5.8%)	4% (-3%, 10%)	1.62 (0.62, 4.22)
Cardiac failure SAE	6 ^a (5.1%)	3 (2.9%)	2% (-3%, 7%)	1.76 (0.45, 6.87)
Deaths	15 (12.7%)	7 (6.7%)	6% (-2%, 14%)	1.89 (0.80, 4.45)
Cardiac deaths	6 (5.1%)	4 (3.8%)	1% (-4%, 7%)	1.32 (0.38, 4.56)
At Week 12				
One or more AE	99 (83.9%)	73 (70.2%)	14% (3%, 25%)	1.20 (1.03, 1.39)
Drug-related AE	9 (7.6%)	5 (4.8%)	3% (-3%, 9%)	1.59 (0.55, 4.58)
Serious AE	63 (53.4%)	50 (48.1%)	5% (-8%, 18%)	1.11 (0.86, 1.44)
Cardiac SAE	21 (17.8%)	9 (8.7%)	9% (0%, 18%)	2.06 (0.99, 4.29)
Cardiac failure SAE	15 ^a (12.7%)	5 (4.8%)	8% (1%, 15%)	2.64 (1.00, 7.03)
Deaths	23 (19.5%)	13 (12.5%)	7% (-3%, 13%)	1.56 (0.83, 2.92)
Cardiac deaths	9 (7.6%)	5 (4.8%)	3% (-3%, 9%)	1.60 (0.55, 4.63)

Text in bold indicate statistical significance.

^a Included one patient on bezlotoxumab with cardiopulmonary failure

^b Calculated during evaluation using RevManv5.3

Source: constructed during the evaluation based on Tables 2-7, Congestive heart failure adverse event attachment submitted with the resubmission.

- 6.20 The resubmission stated that an association between bezlotoxumab and exacerbation of CHF has not been determined. There was no evidence of preclinical cardiac toxicity, the trials did not include CHF as a stratification factor and investigators did not collect information on CHF classification. The subset of patients with CHF at baseline included older patients with more comorbid conditions than the overall trial population, and there were imbalances in baseline characteristics across the arms. The observed difference in the number of deaths was not due to cardiac deaths. The PBAC agreed with the ESC that the signal for possible exacerbation of CHF remained, and that further data are required to evaluate this risk.

Benefits/harms

6.21 A summary of the comparative benefits and harms for bezlotoxumab plus SoC versus SoC alone is presented in Table 8.

Table 8: Summary of comparative benefits and harms for bezlotoxumab and SoC in the trials (total trial populations and high risk subgroups) – Pooled data from MODIFY-I and MODIFY II trials

Benefits						
CDI recurrence at 12 weeks						
Trial	Bez + SoC	SoC	RR (95% CI)	Events/100 patients ^a		RD (95% CI)
				Bez + SoC	SoC	
Total population	129/781	206/773	0.62 (0.51,0.75)	16.5	26.6	-10.0 (-14.0,-6.0)
≥1 of 5 risk factors	100/592	174/583	0.57 (0.46, 0.71)	16.9	29.8	-12.8 (-17.6, -8.0)
≥2 of 4 risk factors	24/146	51/150	0.48 (0.32, 0.74)	16.4	34.0	-16.8 (-26.7, -6.9)
Global cure at 12 weeks						
Total population	496/781	415/773	1.18 (1.09,1.29)	63.5	53.7	9.7 (4.8,14.5)
≥1 of 5 risk factors	371/592	294/583	1.24 (1.12, 1.37)	62.7	50.4	12.1 (6.4, 17.7)
≥2 of 4 risk factors	89/146	71/150	1.29 (1.04, 1.59)	61.0	47.3	12.6 (1.1, 23.9)
Harms						
	Bez + SoC	SoC	RR (95% CI)	Events/100 patients ^a		RD (95% CI)
				Bez + SoC	SoC	
Infusion specific adverse events (e.g. nausea, dizziness, headache, fatigue and pyrexia)						
Total population	81/786 (10)	0/781 ^a	162.0 (21,NA)	10.3	0	10.0 (8.3,12.6)

Shaded areas indicate data previously seen by the PBAC.

Abbreviations: Bez=bezlotoxumab; SoC=standard of care antibiotics; RD=risk difference; RR=risk ratio; NA=not applicable

^a Comparator in practice is no treatment therefore do not expect any infusion related adverse events

Source: constructed during the evaluation.

6.22 On the basis of direct evidence presented by the resubmission, for every 100 patients with who are treated with bezlotoxumab plus SoC in comparison to SoC:

- Approximately 10 fewer patients would have CDI recurrence at 12 weeks.
- Approximately 10 more patients would have global cure at 12 weeks.
- Approximately 10 more patients would experience an infusion specific adverse event.

- 6.23 The ESC and PBAC considered that the possibility of an increased risk of exacerbation of CHF for patients treated with bezlotoxumab plus SoC in comparison to SoC remained.

Clinical claim

- 6.24 The resubmission described bezlotoxumab plus SoC in patients with CDI and ≥ 2 of 4 risk factors, as superior in efficacy for prevention of recurrence and non-inferior in safety compared to SoC alone. This claim was unchanged from the previous submissions.
- 6.25 The PBAC had previously considered that the clinical data supported the claim of superior effectiveness for all patients and patients with ≥ 1 of 4-5 risk factors; however, the overall benefit remained modest and the clinical significance was unclear (paragraph 7.5, Bezlotoxumab November 2017 PSD, and paragraph 7.2, Bezlotoxumab July 2018 PSD).
- 6.26 The clinical data presented in the resubmission also supported the claim of superior effectiveness for patients with ≥ 2 of 4 risk factors; however, the clinical significance of the numerically marginally higher efficacy was unclear for several reasons. The estimated treatment effect for CDI recurrence did not meet the defined MCID; the resubmission did not present any evidence to demonstrate that the observed differences in the risk of CDI recurrence at Week 12 for patients with ≥ 1 of 4 risk factors and ≥ 2 of 4 risk factors was beyond that expected by chance; and, the estimated treatment effect for the more relevant outcome of global cure was similar for patients with ≥ 1 of 5 risk factors and ≥ 2 of 4 risk factors. The PSCR argued that the increased magnitude of benefit reported in the respecified high risk population, relative to the risk reduction reported in patients with ≥ 1 risk factor(s) provided an evidence based rationale to further restrict the patient population. The ESC agreed with the evaluation that the clinical significance of the numerically higher efficacy reported in patients with ≥ 2 of 4 risk factors was unclear and noted that the confidence intervals presented for the small post-hoc subgroup were wide, in comparison to those reported for patients with ≥ 1 of 5 risk factors, and crossed the MCID. The ESC noted that bezlotoxumab is effective in patients with 1 of 4 risk factors (RR=0.60, 95% CI 0.46 to 0.77) and considered it may not be reasonable to excluded these patients. The ESC advised that, while the clinical claim of superior effectiveness was supported for patients with ≥ 2 of 4 risk factors, the respecified high risk patient population was poorly justified biologically and clinically. The ESC considered it unlikely that the updated definition for high risk patients provided a more effective risk stratification algorithm for patients with CDI recurrence than the use of ≥ 1 of 5 risk factors.
- 6.27 Consistent with the previous submissions, the evidence presented in the resubmission did not adequately support the claim of non-inferior safety because the control arm in the trials had a placebo infusion. The PBAC had previously considered that a claim

of inferior comparative safety would be more reasonable because SoC does not require an infusion, and patients treated with bezlotoxumab may suffer additional infusion related AEs (paragraph 7.3; Bezlotoxumab July 2018 PSD). The PSCR argued that the claim of non-inferior comparative safety was reasonable due to the mild/moderate and transient nature of the AEs reported which occurred in a relatively small proportion of patients. The ESC suggested that a claim of inferior comparative safety may be more reasonable due to the reported proportion of bezlotoxumab treated patients who experienced infusion specific AEs (10%) and ongoing concerns regarding a signal for possible exacerbation of CHF.

- 6.28 The PBAC considered that while the claim of superior comparative effectiveness was reasonable for patients with ≥ 2 of 4 risk factors, the overall benefit remained modest with clinical relevance of the benefit unclear.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data as the signal for possible exacerbation of CHF with bezlotoxumab remained.

Economic analysis

- 6.30 The structure of the modelled economic evaluation remained unchanged from the previous July 2018 resubmission, however; the resubmission updated model inputs taking account of most comments made by the PBAC (see below), the revised patient population with ≥ 2 of 4 risk factors, and the lower requested price.
- 6.31 In reference to patients with ≥ 1 of 5 risk factors (or ≥ 1 of 4 risk factors, which was modelled), the PBAC considered that the most informative analysis for decision-making was to apply the following parameters (paragraph 7.6; Bezlotoxumab July 2018 PSD):
- 10-year time horizon;
 - Hazard ratio (HR) for mortality due to CDI 1.12;
 - 2.5% mortality without CDI recurrence;
 - 17.5% CDI recurrence for SoC and 9.8% for bezlotoxumab; and
 - Hospitalisation costs as per AR-DRG (i.e. unadjusted for length of stay).
- 6.32 The updated model included the suggested changes with the exception of the lower recurrence rates. The resubmission argued that the lower CDI recurrence rates proposed by the PBAC were not applicable to patients with ≥ 2 of 4 risk factors, and applied the trial-based rates (34.0% for SoC and 16.4% for bezlotoxumab). This may not be reasonable. Although CDI recurrence rates with SoC may be higher for patients with more risk factors (see Table 6), the resubmission did not present any new evidence to support the applicability of the trial-based results to the Australian population. The PSCR argued that evidence from the MODIFY trials, which included

Australian sites, provides the best available and most robust data to be used in the economic model. Given the limited Australian data available for recurrence, the ESC requested that the sponsor provide data on the recurrence rates from the Australian sites in the MODIFY trials. The pre-PBAC response stated that eight Australian study sites were included in the MODIFY trials, with seven patients recruited from these sites. One of the seven patients met the requested narrower definition of high risk patients. Due to the limited data the pre-PBAC response stated it was not possible to conduct further analyses.

6.33 The PBAC previously recommended that the model apply a lower rate of CDI recurrence for SoC (and use the treatment effect from the trial) because the generalisability of the study population to the Australian population was uncertain and available data suggested that the risk of recurrence in Australia may be lower than in the MODIFY trials (paragraph 6.16, Bezlotoxumab November 2017 PSD). The PSCR noted that the lower CDI recurrence rate for SoC (17.5%) suggested by the PBAC in July 2018 was based on an Australian study (Foster et al, 2014). The PSCR argued that the CDI recurrence rate for SoC reported in the Australian study was not applicable to the respecified high risk population because:

- the rate was based on the proportion of patients with a history of CDI (rather than CDI recurrence rates);
- more than 30% of patients were excluded from the study due to the inability to consent to inclusion (in many instances because the patient was too ill), which will lead to consent bias; and
- the median age was 60.5 years (rather than ≥ 65 years of age), therefore likely reflecting a healthier population relative to the trial sample in the Supportive Analysis.

The ESC agreed with the PSCR that the CDI recurrence rate for SoC reported in the Australian study may not be an appropriate model input in the context of a high risk population. In addition to the points argued in the PSCR the ESC noted that the results were not reported by risk factor status (i.e., the estimated value represents recurrence in all CDI cases, not just those with 1 or 2 or more risk factors). The ESC considered the CDI recurrence rate for SoC reported in the Australian study would therefore likely be an underestimate of the rate for a high risk population.

6.34 The ESC considered that an appropriate CDI recurrence rate for SoC for an Australian high risk population may be higher than the 17.5% proposed by the PBAC in July 2018. As an example, the ESC noted that a 2018 report³ by the Australian Commission on Safety and Quality in Health Care (ACSQHC) cited an aggregate CDI recurrence rate of

³ Australian Commission on Safety and Quality in Health Care (ACSQHC). *Clostridium difficile* infection. Monitoring the national burden of *Clostridium difficile*. ACSQHC, March 2018.

20%, which was similar to the trial-based recurrence rate in patients with no risk factors. The aggregate recurrence rate in the MODIFY trials was 27%. In this example, the ESC considered that an option for the estimation of SoC recurrence rates may be to use the reported difference in recurrence rates by risk factor to estimate recurrence rates by risk factor status from the aggregate recurrence rate cited by the ACSQHC. The process is demonstrated in Table 9, which generates recurrence probabilities of 0.22 and 0.26 for patients with ≥ 1 of 4 and ≥ 2 of 4 risk factors, respectively. The PBAC considered that the CDI recurrence rate for SoC for the Australian population remained uncertain.

Table 9: SoC recurrence rates fitted to aggregate ACSQHC recurrence data

	N	Rec	pr(Rec): trial	pr(Rec): fitted to ACSQHC
All patients	773	206	0.27	0.20
≥ 1 of 4 risk factors subgroup				
0 of 4 risk factors	211	39	0.18	0.14 [^]
≥ 1 of 4 risk factors	562	167	0.30	0.22[^]
Recurrence ratio ($\geq 1:0$ risk factors)			1.61	1.61
≥ 2 of 4 risk factors subgroup				
0 or 1 of 4 risk factors	623	155	0.25	0.19 [^]
≥ 2 of 4 risk factors	150	51	0.34	0.26[^]
Recurrence ratio ($\geq 2:0$ or 1 risk factors)			1.37	1.37

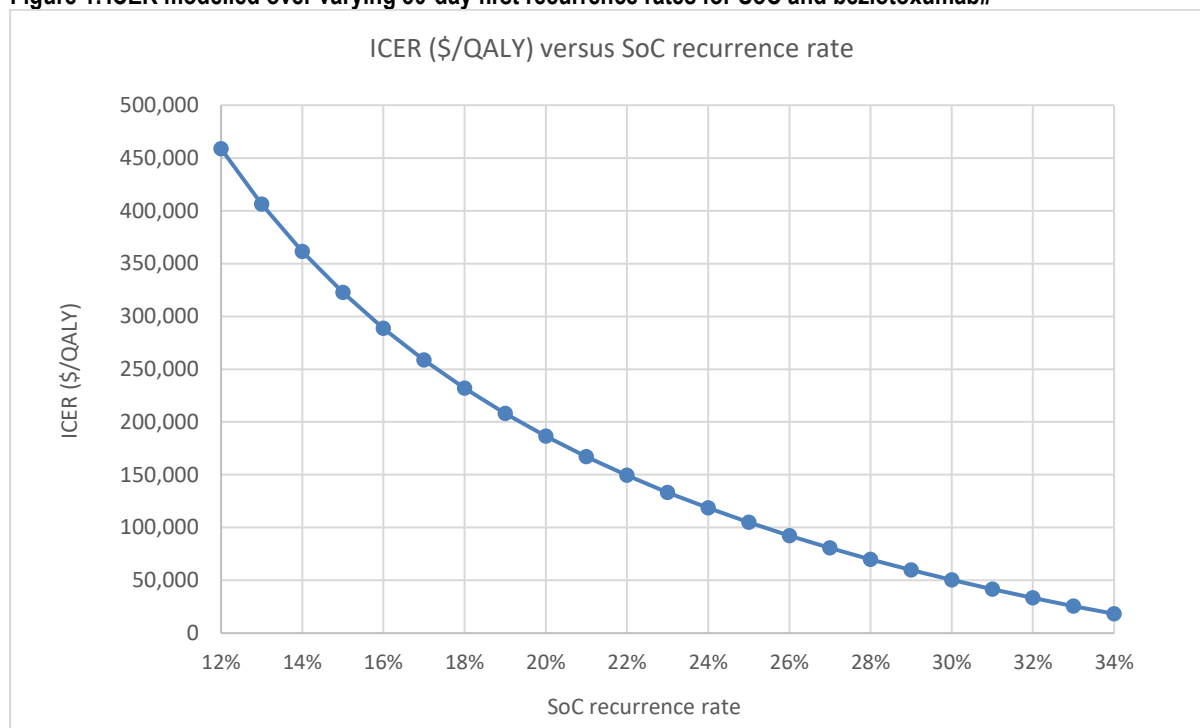
Abbreviations: ACSQHC=Australian Commission on Safety and Quality in Health Care; Rec=recurrence

[^] pr(Rec): trial * 0.75 (0.20 / 0.27) = pr(Rec) fitted to ACSQHC

Source: Constructed during the preparation of the ESC Advice

6.35 The PBAC noted that, the model remained highly sensitive to CDI recurrence rates, illustrated in Figure 1.

Figure 1: ICER modelled over varying 30-day first recurrence rates for SoC and bezlotoxumab#



Abbreviations: CDI=Clostridium difficile infection; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted lifeyears; SoC=standard of care

Source: constructed during the evaluation from Bezlotoxumab Sec 3 Workbook of the resubmission.

The recurrence rate for bezlotoxumab was estimated assuming a relative risk of 0.48 for bezlotoxumab versus SoC, derived from CDI recurrence rates in the MODIFY subgroup with ≥ 2 of 4 risk factors.

- 6.36 The resubmission also updated other model parameters including patient characteristics (age and gender), the probability of severe CDI recurrence and the proportion of mild/moderate CDIs requiring hospitalisation, based on data reported for patients with ≥ 2 of 4 risk factors in the MODIFY trials. These ESC considered that these changes may be reasonable if a target population of patients with ≥ 2 of 4 risk factors of CDI recurrence is accepted. However, the ESC considered that the re-estimated parameters may not be appropriate if a target population of patients with ≥ 1 of 4 risk factors was accepted.
- 6.37 The resubmission assumed no patients weigh >100 kg and therefore no patients required two vials of bezlotoxumab. The ESC considered that the assumption that no patients weigh >100 kg was not supported by the trial data, and favoured bezlotoxumab.
- 6.38 The assumed utility values in the model were unchanged from the previous submissions. The PBAC had previously noted that the model was not very sensitive to utility assumptions alone (Table 9 p14, Bezlotoxumab November 2017 PSD). This remained the case with the revised model in this resubmission.
- 6.39 Table 10 presents a stepped analysis showing the decrease in the ICER with sequential changes to the model parameters from those in the previous submission. The

reference case including all of the PBAC recommended parameters in the previous submission resulted in an ICER of approximately more than \$200,000/QALY.

Table 10: PBAC reference case ICER and impact on ICERs of changing additional parameters

Scenario	Variables	ICER (cost/QALY)
July 2018 model population: patients with ≥1 of 4 risk factors		
A (reference case PBAC)	<ul style="list-style-type: none"> • HR for mortality due to CDI 1.12 • 2.5% mortality without CDI recurrence • Hospitalisation costs as per AR-DRG • Recurrence rates for SoC (17.5%) and bezlotoxumab (9.8%) <ul style="list-style-type: none"> ○ Submitted model: 34% and 16.4% • 12.2% of recurrences are severe <ul style="list-style-type: none"> ○ Submitted model: 15.7% • 32% of mild/moderate CDI requiring hospitalisation <ul style="list-style-type: none"> ○ Submitted model: 40.5% • Age 68.1 years; 55.8% females; 22.7% severe CDI at baseline <ul style="list-style-type: none"> ○ Submitted model: 75.4 yrs, 57.4% and 44.3% • 7.3% patients weighing >100 kg <ul style="list-style-type: none"> ○ Submitted model: 0% • Bezlotoxumab \$██████ per vial • Time horizon 10 years 	██████
B = A + new price in current resubmission	<ul style="list-style-type: none"> • HR for mortality due to CDI 1.12 • 2.5% mortality without CDI recurrence • Hospitalisation costs as per AR-DRG • Lower recurrence rates for SoC (17.5%) and bezlotoxumab (9.8%) • 12.2% of recurrences are severe • 32% of mild/moderate CDI requiring hospitalisation • Age 68.1 years; 55.8% females; 22.7% severe CDI at baseline • 7.3% patients weighing >100 kg • Bezlotoxumab \$██████ per vial • Time horizon 10 years 	██████
Revised model population: patients with ≥2 of 4 risk factors		
C = B + updated recurrence rates	<ul style="list-style-type: none"> • Recurrence rates for SoC changed from 29.7% in July 2018 resubmission to 34% and bezlotoxumab from 16.7% to 16.4% 	██████
D = C + updated % severe recurrence	<ul style="list-style-type: none"> • % of recurrences that are severe changed from 12.2% in July 2018 resubmission to 15.7% 	██████
E = D + updated % mild/mod CDI with hospitalisation	<ul style="list-style-type: none"> • % of mild/moderate CDI requiring hospitalisation changed from 32% in July 2018 resubmission to 40.5% (120/296) 	██████
F = E + updated age, gender and % severe CDI at baseline	<ul style="list-style-type: none"> • Age from 68.1 to 75.4 years; proportion female from 55.8% to 57.4%; proportion severe CDI from 22.7% to 44.3% in the July 2018 resubmission to the current resubmission respectively 	██████
G = F + updated % >100 kg (≡ % requiring 2 vials)	<ul style="list-style-type: none"> • Proportion >100 kg reduced from 7.3% in July 2018 resubmission to 0% 	██████

Abbreviations: CDI=clostridium difficile infection; HR=hazard ratio; SoC=standard of care
 Source: constructed during the evaluation

- 6.40 The higher CDI recurrence rates based on the MODIFY subgroup of patients with ≥ 2 of 4 risk factors and lower requested price were the key parameters that reduced the ICER from more than \$200,000 /QALY (PBAC reference case for ≥ 1 of 4 risk factors) to \$20,000 (resubmission base case for ≥ 2 of 4 risk factors). Changing price alone reduced the ICER to more than \$200,000/QALY, while also changing CDI recurrence rates reduced the ICER to \$45,000 - \$75,000 /QALY. Slight differences in patient characteristics and other parameters for the ≥ 2 out of 4 versus ≥ 1 out of 4 subgroups (which influenced costs and cost-offsets) resulted in the resubmission’s base case of around \$15,000-\$45,000/QALY.
- 6.41 Key drivers of the economic evaluation are summarised in Table 11. The table does not include time horizon, mortality rates or hospitalisation cost because the model applied estimates recommended by the PBAC.

Table 11: Key drivers of the model in the resubmission

Description	Method/Value	Impact
CDI recurrence rate for SoC	The 30-day first CDI recurrence rate for SoC and bezlotoxumab were informed by results of post-hoc subgroup analysis of the MODIFY trials (≥ 2 of 4 risk factors). The model was very sensitive to this assumption. Assuming the PBAC-recommended recurrence rates (SoC 17.5% and bezlotoxumab 9.8%), the ICER increased from ~\$15,000 - \$45,000/QALY to more than \$200,000 /QALY.	Very High Favoured bezlotoxumab
Proportion of recurrences which are severe	Informed by results of post-hoc subgroup analysis of the MODIFY trials (≥ 2 of 4 risk factors). The revised model was moderately sensitive to this variable. Salavert et al (2018) reported that this parameter varied widely across subgroups, from 5% in the subgroup of patients with ≥ 1 episode of CDI in previous 6 months, to 42% in the subgroup with severe CDI (Table 1 of Salavert et al 2018). Hence, the proportion of severe CDI recurrences in practice may depend on the number and type of risk factors present in the Australian population.	Moderate Favoured bezlotoxumab
Proportion of mild/moderate CDI requiring hospitalisation	Informed by post-hoc subgroup analysis of the MODIFY trials (≥ 2 of 4 risk factors). The revised model was moderately sensitive to this variable.	Moderate Favoured bezlotoxumab
Proportion of bezlotoxumab patients >100 kg	0% assumption. Resubmission’s justification was that the population with ≥ 2 of 4 risk factors is likely to be elderly with comorbidities. This was not appropriate. In the MODIFY trials, 4.4% of patients with ≥ 2 of 4 risk factors weighed >100kg compared to 7.3% for patients with ≥ 1 of 5 risk factors. The revised model was moderately sensitive to this variable.	Moderate Favoured bezlotoxumab

Source: Constructed during the evaluation.

- 6.42 Table 12 summarises the results of the stepped economic evaluation for the population with ≥ 2 of 4 risk factors in this resubmission. The base case ICER was \$15,000-\$45,000/QALY for patients with ≥ 2 of 4 risk factors of CDI recurrence.

Table 12: Results of the stepped economic evaluation in this resubmission

Step and component	Bezlotoxumab + SoC	SoC only	Increment
Step 1: Used subpopulation ≥ 2 of 4 risk factors from MODIFY I and MODIFY II			
Costs	██████████	\$0	██████████
Outcomes (CDI recurrence rate)	16.4%	34.0%	-17.6%
Cost per CDI recurrence avoided			██████████
Step 2: Used Markov model to determine life years			
Costs	██████████	██████████	██████████
Outcomes (life years)	5.6734	5.6613	0.0122
Cost per life year gained			██████████
Step 3: Applied utility weights to Markov model to determine QALYs			
Costs	██████████	██████████	██████████
QALYs	4.3320	4.3202	0.0118
Cost per QALY gained (base case)			
			██████████

Shaded areas indicate data previously seen by the PBAC.

Abbreviations: SoC=standard of care; QALY=quality adjusted life years

Source: Table 3-23, p135 and Bezlotoxumab Sec 3 Workbook of the resubmission

- 6.43 The base case ICER in the resubmission was highly sensitive to the assumed CDI recurrence rates and other parameters associated with the magnitude of hospitalisation cost-offsets as well as drug costs. Given considerable uncertainty around these parameters, particularly whether CDI recurrence rates reported in the MODIFY trials were applicable to the Australian clinical setting, the base case ICER was highly uncertain.
- 6.44 The ESC noted that a sensitivity analysis assuming a CDI recurrence rate of 26% for SoC for patients with ≥ 2 of 4 risk factors for CDI recurrence (see paragraph 6.37) and 12.5% for bezlotoxumab (based on a RR of 0.48) increased the ICER from \$15,000-\$45,000 /QALY in the base case to \$75,000-\$105,000 /QALY. The pre-PBAC response stated that taking into account the lower effective price proposed in the response (DPMQ of \$██████████) and the ESC’s advice for the respecified high-risk population, where the CDI recurrence rate for SoC is assumed to be 26% and 12.5% for bezlotoxumab (based on a RR of 0.48) the resulting ICER is \$15,000-\$45,000/QALY.
- 6.45 The ESC considered the previously defined population of patients with ≥ 1 risk factors for CDI recurrence may be more appropriate. The ESC advised that it may be reasonable for the base case specified by PBAC in July 2018 to be used, with the possible exception of the nominated 17.5% recurrence rate for SoC, which the ESC considered likely underestimated recurrence for a high risk population. The ESC noted that when the recurrence rate for SoC estimated from the ASQHC example is used (22%) (see paragraph 6.37), the PBAC reference case ICER (see Table 10) for patients with ≥ 1 risk of 4 factors is reduced from approximately more than \$200,000 /QALY at the requested price (██████████ per vial) to approximately more than \$200,000 /QALY (assuming 12.3% recurrence rate for bezlotoxumab based on a RR of 0.56).

Drug cost/patient/course

6.46 The average cost of bezlotoxumab was assumed to be \$ [REDACTED] per patient per course (effective price, private hospital use), assuming a single vial of bezlotoxumab 1000mg was required. Table 13 compares drug costs between the trial, model and financial estimates.

Table 13: Drug cost per patient for bezlotoxumab (1000mg vial)

	Trials	Model	Financial estimates
Mean dose (mg)	730mg ^a administered	1000mg costed	1000mg costed
Mean duration	Single dose	Single dose	Single dose
Cost/patient	-	[REDACTED]	[REDACTED]
Cost/patient/course	-	[REDACTED]	[REDACTED]

effective price, private use

[^] The requested effective price (private) assumed a ready prepared dispensing fee of \$7.15; the current dispensing fee (since January 2019) is \$7.29, resulting in an effective price (private) of [REDACTED].

^{*} Although the resubmission stated the financial estimates assumed repeat dosing of bezlotoxumab in recurrent episodes (either treated or untreated) from the prior year, however the estimates presented in Section 4 spreadsheet indicated that it did not account for repeat dosing with bezlotoxumab for CDI recurrence beyond 90 days of the index episode.

^a Derived from Appendix 2.7.3-rcdi:19, p214 of MSD rCDI Integrated Analysis

6.47 The Pre-PBAC response proposed a reduced effective price of bezlotoxumab from a DPMQ (public hospitals) of [REDACTED] to [REDACTED].

Estimated PBS usage & financial implications

6.48 The resubmission was not considered by DUSC; however, DUSC considered the November 2017 submission. Consistent with the previous submissions, this resubmission used an epidemiological approach to estimate the financial impact of listing bezlotoxumab on the PBS.

6.49 The PBAC had previously considered that the financial estimates were highly uncertain and likely an underestimate for several reasons including the derivation of the eligible population from oral vancomycin scripts on the PBS, which only accounted for approximately 10% of CDI related diarrhoeas (paragraphs 6.47 and 6.48; Bezlotoxumab July 2018 PSD). The resubmission did not address any of the PBAC's concerns. The methodology and assumptions used to estimate the financial impact of listing bezlotoxumab on the PBS were largely unchanged from the previous submission with a few minor exceptions: assuming that the proportion of patients >100 kg was 0%, and updating CDI recurrence rates as well as the proportional use of metronidazole based on the MODIFY subgroup with ≥2 of 4 risk factors.

6.50 The number of eligible patients remained similar to the previous submissions, despite the resubmission requesting a much narrower listing (patients with ≥2 of 4 risk factors compared to ≥1 risk factor of 5 risk factors). In the trial evidence, 76% of patients enrolled in the MODIFY trials had ≥1 of 5 risk factors compared to 19% with ≥2 of 4 risk factors.

6.51 Table 14 presents the estimated use and financial implications of listing bezlotoxumab on the PBS.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■	■	■	■	■	■
Number of infusions/vials dispensed ^a	■	■	■	■	■	■
Estimated financial implications of bezlotoxumab						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
Estimated financial implications for vancomycin^b						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
Net financial implications (current resubmission)						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS	■	■	■	■	■	■
Previous July 2018 resubmission						
Number of patients treated	■	■	■	■	■	■
Number of infusions/vials dispensed ^c	■	■	■	■	■	■
■	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS	■	■	■	■	■	■

Shaded areas indicate data previously seen by the PBAC.

Abbreviations: CDI=*Clostridium difficile* infection;

^a Assuming 0% of patients use 2 bezlotoxumab vials as assumed by the current resubmission.

^b The evaluation corrected for the PBS utilisation data in 2018 (instead of 2016 as used by the resubmission). Assuming that 70% of all vancomycin scripts will be 125mg (DPMQ: \$262.48) and the remaining 30% will be 250mg (DPMQ: \$518.87) based on 2018 data, the average co-payment for vancomycin avoided for PBS changed from \$17.32 to \$17.27 and RPBS changed from \$5.32 to \$5.85.

^c Assuming 7.3% of patients use 2 bezlotoxumab vials as assumed by the July 2018 resubmission.

Source: Constructed during the evaluation from Section 4 and Bezlotoxumab Sec 4 Workbook of the resubmission

6.52 The resubmission estimated the total cost to the Government in the first 6 years of bezlotoxumab listing on the PBS was \$60-\$100 million, compared to \$60-\$100 million in the July 2018 resubmission (a 25.6% decrease). The difference was largely due to the ■% reduction in the requested price.

6.53 The financial estimates remained sensitive to the assumptions used to derive the eligible population including uptake rates, CDI recurrence rate and ratio of vancomycin to metronidazole use. Whether the financial estimates were an under- or overestimate for the treatment of patients with ≥2 of 4 risk factors was unknown given the resubmission did not make any adjustment for the fact that not all patients with CDI have ≥2 of 4 risk factors of CDI recurrence. The ESC noted that in the MODIFY trials the use of the post-hoc subgroup of patients with ≥2 of 4 risk factors reduced the

sample size significantly. The ESC considered that the financial estimates remained highly uncertain.

- 6.54 The risk of bezlotoxumab use beyond the requested restriction was considerable. The clinical trials demonstrated similar efficacy for patients with any risk factors (e.g. ≥ 1 risk factor), whereas the requested restriction limits use to patients with ≥ 2 of 4 risk factors. Should 'high risk' status be determined at the discretion of the treating clinician, clinicians might treat (or retreat) more patients given bezlotoxumab was easy to administer and well tolerated in the trials.

Quality Use of Medicines

- 6.55 No quality use of medicines information was presented in the resubmission.

Financial Management – Risk Sharing Arrangements

- 6.56 The resubmission proposed a special pricing arrangement with an effective price for bezlotoxumab of [REDACTED] per vial (public hospitals) (versus a published price of \$4,365). The Pre-PBAC response stated the sponsor was willing to reduce the effective price of bezlotoxumab from a DPMQ (public hospitals) of [REDACTED] to [REDACTED] (versus a published price of \$4,365).
- 6.57 In addition to the special pricing arrangement, the Sponsor proposed a risk sharing arrangement with a cap/rebate structure to account for any uncertainty associated with uptake and repeat dosing. The cap structure was based on the base case utilisation estimates presented in the resubmission up to Year 3, with the caps remaining at the Year 3 estimate for Year 3 to Year 5. The Sponsor proposed a [REDACTED]% rebate for incremental payments over the cap. The PSCR indicated that the proposed risk-sharing arrangement would also account for any need for a second vial in patients who weighed >100 kg. The pre-PBAC response confirmed the sponsor was willing to enter into the risk sharing arrangement outlined in the resubmission at the reduced effective DPMQ (public hospital) of [REDACTED].

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of bezlotoxumab on the PBS for the prevention of *Clostridium difficile* infection (CDI) on the basis of the proposed patient population being inadequately justified, its modest effectiveness, and concerns regarding safety, along with a high and uncertain incremental cost-effectiveness ratio (ICER) and uncertain financial estimates.
- 7.2 The PBAC considered that the requested listing for high risk patients with ≥ 2 of 4 risk factors of CDI infection, compared to ≥ 1 of 5 risk factors (or ≥ 1 of 4 in the modelled economic evaluation) in the July 2018 resubmission was poorly justified clinically and epidemiologically. The PBAC noted the numerically larger observed difference

reported in CDI recurrences at week 12 for patients with ≥ 2 of 4 risk factors (RD: -16.8% (95%CI: -26.7, -6.9)), compared to patients with ≥ 1 of 5 risk factors (RD: -12.8% (95%CI: -17.6, -8.0)). However, the PBAC considered the clinical significance of the numerically higher difference reported for the small post-hoc subgroup was uncertain due to the imprecise estimate (wide confidence intervals that crossed the MCID) and was not statistically different to that reported for patients with ≥ 1 of 5 risk factors. The PBAC therefore agreed with the ESC that it was unlikely that the updated definition for 'high risk' patients provided a more effective risk stratification algorithm for patients with CDI recurrence than the use of ≥ 1 of 5 risk factors.

- 7.3 In addition, the PBAC noted that of the four risk factors included in the resubmission's definition of patients at 'high risk' of CDI recurrence, only age ≥ 65 years and history of CDI in the past 6 months were associated with an increase in the risk of CDI recurrence in the MODIFY trials. For the other two risk factors (immunocompromised, clinically severe CDI) there was no robust evidence of an increase in the risk of recurrence. The PBAC advised that the prognostic value of each of the risk factors used in the risk stratification process was likely to be of greater importance than whether patients had ≥ 2 of 4 risk factors or ≥ 1 of 5 risk factors.
- 7.4 The PBAC recalled that the MODIFY trials showed no evidence of a mortality benefit associated with bezlotoxumab compared to SoC. The PBAC also noted that subsequent lines of antibiotic therapy, and in some instances faecal microbiota transplantation, were available for the treatment of recurrent CDI. The PBAC reiterated its previous advice that the overall benefit of bezlotoxumab remained modest and was limited to a small difference in the prevention of CDI recurrence.
- 7.5 The PBAC noted, for the subset of patients in the MODIFY trials with a history of CHF at baseline, that the number of cardiac failure serious adverse events was higher in the bezlotoxumab arm than in the placebo arm (RD: 8% (95% CI 1%, 15%)). The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data provided in the resubmission as the possibility of an increased risk of exacerbation of CHF for patients treated with bezlotoxumab in comparison to SoC remained.
- 7.6 The PBAC noted the base case ICER in the resubmission was highly sensitive to the assumed CDI recurrence rates and considered that the recurrence rates used in the economic model (difference of approximately 18%) were not consistent with data from the MODIFY trials (difference of approximately 10%). The PBAC further noted that the ICER was uncertain due to the assumed mortality benefit not being supported by the trial data and the reduced efficacy in the trials in patients aged less than 65 years. The PBAC noted the lower effective price proposed in the pre-PBAC response, however considered the resulting ICER unreliable for the aforementioned reasons.
- 7.7 The PBAC recalled that it in July 2018 it had considered the financial estimates to be highly uncertain and likely an underestimate. The PBAC noted that the number of

eligible patients remained similar to the July 2018 submission, despite the resubmission requesting a much narrower listing (patients with ≥ 2 of 4 risk factors compared to ≥ 1 of 5 risk factors), and considered that this further increased the uncertainty of the estimates. The PBAC considered that the potential for use beyond the requested population (i.e. ≥ 2 of 4 risk factors) was considerable given clinical data demonstrated bezlotoxumab was effective at treating CDI recurrence for patients with any risk factors (e.g. ≥ 1 of 5 risk factors), easy to administer and well tolerated. The PBAC considered that, despite the lower effective price proposed in the pre-PBAC response, the estimated financial impact of bezlotoxumab remained high in the context of the modest clinical benefit.

- 7.8 The PBAC noted the pre-PBAC response confirmed the sponsor was willing to enter into the risk sharing arrangement outlined in the resubmission at the lower effective price proposed in the response. The PBAC considered that a ████% rebate for incremental payments over a cap was appropriate, however, the proposed expenditure levels were not accepted given the estimated use was uncertain and the proposed price was not considered cost-effective.
- 7.9 The PBAC proposed that any future resubmission should be a major submission. The PBAC considered that such a resubmission should restrict the proposed PBS population to those aged ≥ 65 years and/or with a history of CDI in the past 6 months. In addition, the cost-effectiveness should be informed by more reliable estimates of the risk of CDI recurrence, and the uncertainty associated with the assumed mortality benefit and efficacy in younger patients should be addressed. The PBAC advised that the uncertainty associated with the financial estimates would need to be addressed, including with a risk sharing arrangement with a 100% rebate over the financial caps.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

MSD is disappointed in the PBAC outcome and will continue working to provide access for Australian patients with CDI.