7.01 BEZLOTOXUMAB, Solution concentrate for I.V. infusion 1000 mg in 40 mL, Zinplava®, Merck Sharp & Dohme

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 oral antibiotics.

1.2 This was a second submission for bezlotoxumab for prevention of CDI. The PBAC previously rejected an application at the November 2017 PBAC meeting on the basis of its modest effectiveness and uncertain incremental cost-effectiveness ratio (ICER).

1.3 As with the previous submission, 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 it is true that no PBS listed treatments are available to prevent CDI recurrence, subsequent lines of antibiotic therapy are available for treatment of recurrent CDIs. In that sense, bezlotoxumab would be delaying or reducing the need for patients to access subsequent lines of antibiotics for treatment of CDI.

1.4 The basis for the resubmission's requested listing was cost-effectiveness of bezlotoxumab plus standard of care (SoC) versus SoC alone.

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

Component	Description
Population	Patients aged 18 year or older with confirmed diagnosis of toxin B positive CDI, who are at high risk of CDI recurrence and receiving oral antibiotics.
Intervention	Bezlotoxumab 1000mg IV single administration.
Comparator	SoC antibiotic therapy including but not limited to vancomycin / metronidazole.
Outcomes	Prevention of recurrence of CDI and reduction in hospitalisations due to CDI recurrence.
Clinical claim	In patients with CDI, bezlotoxumab with SoC is more effective than SoC antibiotics at preventing recurrence of CDI infection with a similar safety profile.

Abbreviations: CDI=*clostridium difficile* infection; IV=intravenous; SoC=standard of care
Source: Table 1-2, p13 of the resubmission

2 Requested listing

Secretariat suggested additions are in italics and deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Bezlotoxumab, concentrated vial for injection, 1000mg/40mL	1	0	published prices $[redacted] (public) $[redacted] (private) effective price $[redacted] (public) $[redacted] (private)	Zinplava	Merck Sharp & Dohme

Category / Program	Section 100 – Authority Required
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
PBS Indication:	Clostridium Difficile Infection
Treatment phase:	Initial
Restriction Level / Method: Section 100 (Authority required)	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Patient~~s~~ must be receiving oral antibiotic therapy
Clinical criteria:	Patient~~s~~ must have confirmed toxin B positive Clostridium Difficile Infection AND Patient must be at high risk of recurrence.
Prescriber Instructions	High risk is defined by the presence of one or more of the following factors: Age 65 years or older, history of ~~CDI~~ *Clostridium Difficile Infection* in the past 6 months, clinically severe ~~CDI~~ *Clostridium Difficile Infection*, hypervirulent strain (027, 078, or 244 ribotypes), or compromised immunity
Administrative Advice	Repeat administration is not permitted within 90 days of the initial episode.

2.1 The proposed effective price (via special pricing arrangement) for bezlotoxumab was $[redacted] (public hospitals) (versus a published price of $[redacted]). This was a [redacted]% price reduction compared to the November 2017 submission.

2.2 The resubmission presented a revised requested restriction for bezlotoxumab. The requested restriction was consistent with the TGA approved indication of bezlotoxumab. Compared to the restriction considered at the November 2017 PBAC meeting, the main changes were:

- Patients must have confirmed toxin B positive CDI as bezlotoxumab confers passive immunity to toxin B;
- High risk of CDI recurrence is to be a clinical practice decision, however under "Prescriber instructions" high risk is defined by the presence of one or more of the following factors: age >65 years, history of CDI in the past 6 months, clinically severe CDI, immunocompromised patient, or infection with a hypervirulent strain (027, 078, 244 ribotypes).

- Repeat dosing of bezlotoxumab is now permitted 90 days after the initial episode, whereas previously, via the PSCR[1] it was proposed that bezlotoxumab be limited to once per patient lifetime. Despite the incorporation of repeat administration with bezlotoxumab in the requested restrictions, repeat dosing was not captured in the modelled economic evaluation or the financial estimates. Instead, the resubmission continued to argue that there was no reason to expect the efficacy and cost effectiveness of bezlotoxumab to differ upon re-administration. The PSCR acknowledged that the efficacy and safety of bezlotoxumab re-administration was unknown. The sponsor indicated it would be willing to manage the uncertainties around the cost-effectiveness of repeat dosing. Suggestions presented in the PSCR include: "monitoring repeat dosing via a unique authority code, which would have different rebates associated with it; or restricting use to once per lifetime (as per the November 2017 submission) until further evidence around repeat dosing becomes available".

2.3 The PBAC considered that given there is no clinical data to support repeat dosing of bezlotoxumab, and that it had not been accounted for in the economic analysis, that it may be more appropriate to limit use to one dose per lifetime in the restriction. However, the PBAC also noted that the risk of use outside this limit would also need to be managed through a risk sharing arrangement.

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

3 Background

Registration status

3.1 Bezlotoxumab was approved by the TGA (8 November 2017) after the November 2017 PBAC meeting for the indication of: "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 antibiotic 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."

3.2 The approved Australian indication aligns with both the EU and US market authorisations for bezlotoxumab and is limited to patients at a high risk of CDI recurrence. The factors associated with a high risk of CDI recurrence however were not stated in the TGA restriction wording.

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

[1] Note the wording in the requested listing presented in the submission did not prohibit use of bezlotoxumab for subsequent infections. Post evaluation, the PSCR proposed the restriction could limit to single lifetime use.

Previous PBAC consideration

3.3 A summary of outstanding matters from the November 2017 PBAC consideration of bezlotoxumab and how they were addressed in the resubmission is presented in the table below. Briefly, the PBAC noted the modest efficacy of bezlotoxumab at preventing CDI recurrence and noted that it was only marginally higher in the 'high risk' patient subgroup. The PBAC also thought the cost effectiveness of bezlotoxumab to be uncertain, the Committee considered mortality rates and mortality benefits of bezlotoxumab were overestimated in the economic model, while other important patient and health-system relevant benefits, such as a reduction in hospital bed days and impact on quality of life, which may be realised as a result of the reduction in CDI recurrence were not accounted for in the model.

Table 2: Key differences between the November 2017 submission and the resubmission

Component	Submission considered in November 2017 *PBAC recommendations in italics*	Current resubmission
Requested restrictions		
Population	Patients with severe first episode or recurrent CDI. In the PSCR a revised listing restricting use to "High risk" population was further proposed. *The PBAC noted that the efficacy of bezlotoxumab was numerically marginally higher in the 'high risk' group of patients, but noted the considerable overlap in confidence intervals across patient subgroups. It considered that it may be more appropriate for the determination of patients at high risk to be a clinical practice decision, rather than as specific criteria in the restriction. However, the PBAC advised that as bezlotoxumab conferred passive immunity to toxin B, the restriction should require patients to be confirmed toxin B positive.*	Patients at 'high risk' of CDI recurrence as determined by clinicians, with confirmed toxin B positive CDI.
Suggested use	One dose administered per patient in a lifetime. *The PBAC considered it was probable, and likely appropriate, that bezlotoxumab would be used more than once within a patient's lifetime for a new infection or recurrence.*	Bezlotoxumab was administered once per episode of CDI. Repeat dosing was only permitted after 90 days of initial episode. *Inappropriately, this was not captured in the modelled economic evaluation.*
Patient location	Outpatient subgroup. *The PBAC did not agree with the submission that the outpatients' subgroup, was representative of the PBS population, and considered that future analyses should be based on the total population.*	Patients at 'high risk' of CDI recurrence inclusive of inpatients and outpatients
List price	$[redacted] per 1000mg/40mL vial	$[redacted] per 1000mg/40mL vial, representing a [redacted]% price reduction. Request for this to be applied as a special pricing arrangement.
Clinical evaluation		

Component	Submission considered in November 2017 *PBAC recommendations in italics*	Current resubmission
Clinical efficacy	The main efficacy results were informed by the outcomes of the MODIFY I and MODIFY II trials of bezlotoxumab +SoC antibiotics versus SoC antibiotics alone. *The submission had focused on a trial defined 'outpatient group', which it claimed to represent treatment of CDI in an outpatient patient setting. This was an inappropriate claim, instead 'outpatient' represented the location of diagnosis of CDI of trial participants.* The primary outcome found a modest reduction in CDI recurrence at 12 weeks in all participants (RD: -10.1%, 95%CI: -14.2, -6.1). Data presented in the PSCR illustrated that the risk of CDI recurrence in the high risk population was -[redacted]% (95%CI: [redacted], [redacted]). *The PBAC considered the overall benefit of bezlotoxumab in high risk group (data presented in PSCR) remained modest, and the clinical significance of such a benefit was unclear.*	Data from the high risk population was again presented in the resubmission, showing a CDI recurrence rate reduction of [redacted]% (95%CI: [redacted], [redacted]). Data presented in Gerding *et. al.* 2018 illustrated no significant benefit of bezlotoxumab in patients without any risk factor for recurrence (RD (95%CI): -2.1(-11.1, 6.9), but the benefit significantly increases if there were ≥3 risk factors (RD (95%CI): -24.8 (-39.1,-9.3).
Outcome measure	CDI recurrence the primary outcome in the MODIFY trials. *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. Global cure is also less biased compared to CDI recurrence, since by definition, CDI recurrence would underestimate the true recurrence rate (since those who fail antibiotic therapy and do not get better from their current CDI episode cannot have a recurrence).*	Global cure rate in high risk patients was reported in addition to CDI recurrence, BUT *global cure results were not used in either the modelled economic evaluation or financial estimates, both of which continued to rely on CDI recurrence.*
Safety	*The PBAC did not accept the submission's non-inferiority safety claim versus SoC antibiotics and considered that the total proportion of infusion specific AEs for bezlotoxumab, rather than the difference compared to placebo, was the more reasonable estimate of the AE rate (since placebo arm of trial had received placebo infusions).*	The resubmission maintained a claim of non-inferior safety, stating that while the 10% of patients in the bezlotoxumab arm of the trial had infusion specific AEs, the majority of the events were mild in nature. Modelled economic evaluation included health care cost for infusion specific AEs from bezlotoxumab administration (based on 10% infusion reactions in the bezlotoxumab arm from MODIFY trials).
Economic modelling		
Patient population	Outpatient population (based on MODIFY trials) Age at model entry: 56.7 Proportion of females: 63.3 Entering with severe CDI: 3.6	High risk population based on MODIFY I and II trial subgroups. High risk was defined by the resubmission as having at least one of the following risk factors: age ≥ 65 or history of CDI in the past 6 months, immunocompromised or severe CDI)[c]. Age at model entry: [redacted] Proportion of females: [redacted]% Entering with severe CDI: [redacted]%

Component	Submission considered in November 2017 *PBAC recommendations in italics*	Current resubmission
Model structure	A stepped cost utility analysis was presented, based on results from the MODIFY I and MODIFY II trials. The model presented was a Markov cohort model with a 10-year time horizon. There were 8 main health states in the model: mild/moderate CDI; severe CDI; clinical cure; clinical failure; post-clinical failure; colectomy; post colectomy and death. Clinical failure and colectomy are temporary health states and patients were assumed to transit to post clinical failure and post colectomy next cycle. A cycle length of 15 days was adopted in Year 1, annual cycle lengths thereafter. The model was calibrated to adjust 84- and 30-day outcomes to 15 days. *The PBAC reflected that the submission's model was unnecessarily complicated, and any resubmission should take a more simplified approach for modelling any mortality benefit, and should also take into account other benefits.* *The PBAC considered that there were considerable benefits to preventing recurrence in terms of quality of life and other health-system benefits, which had not been modelled.*	The model structure was similar to the model presented in the November 2017 submission with a few modifications: • Cycle length in Year 1 was increased to 30-days. • Calibration of outcomes was removed. • Colectomy health state was also removed • Additional cost benefit of avoiding CDI infections were included in the form of hospital bed days avoided. *However, the model was still driven by mortality, which the PBAC had previously considered was not the main benefit associated with bezlotoxumab in the Australian context.*

Component	Submission considered in November 2017 *PBAC recommendations in italics*	Current resubmission
Mortality rate	The trial reported no significant differences in mortality. Mortality rates were obtained from Olsen *et. al.* (2015) based on US data. • 180-day all-cause mortality (no recurrences): 25.7% (adjusted to 15-day mortality 0.0245) • 180-day all-cause mortality (recurrences): 36.3% (adjusted to 15-day mortality 0.0391) • Hazard ratio mortality (calibrated): 1.6 *The PBAC noted that the mortality estimates used from US and EU were not comparable to Australia and not supported by published Australian data or the views expressed by the clinician in the Sponsor hearing.* *One Australian study (Huber et. al. 2014) identified during the evaluation estimated a 30 day mortality rate of 3.6%, which is significantly lower than that reported by Olsen 2015 at 30 days of 8.7% and 7.8% or 25.7% and 36.3% at 180 days.* *The ESC noted that a RR for mortality of 1.6 was applied to patients with recurrent CDI compared to non-recurrent CDI patients, which was higher than reported in the study used to inform the RR (adjusted HR of 1.33: 95% CI 1.12 to 1.58), which was in itself likely an overestimate. The model also assumed a higher mortality rate in the comparator arm than likely to be the case in the eligible Australian population. The ESC considered that a more appropriate approach would be to apply the lower 95% CI for the recurrent CDI hazard ratio for mortality (1.12) to estimate the mortality effect.*	30-day all-cause mortality for no recurrences, (Huber *et. al.* 2014): 3.6% Hazard ratio mortality (Olsen et a; 2015): 1.33 (*Note this HR was higher than what ESC had considered more reasonable 1.12, the lower 95CI reported by Olsen et. al. 2015).*
Cost of bezlotoxumab	Bezlotoxumab + administration: $[redacted] Assumed 10% of patients (weight>100kg) will need 2 vials	Bezlotoxumab + administration*: $[redacted] (including a [redacted]% price reduction for bezlotoxumab). Assumed 7.3% of patients (weight>100kg) will need 2 vials. *10% of patients in the bezlotoxumab arm were assumed to have an infusion related AE (based on trial results) that will require one additional specialist visit.
Resource cost	Mild/moderate CDI^: $4,443.69# Severe CDI: $30,890.70 ^ Proportion of patients with mild/moderate CDI requiring hospitalisation: 32%#	Mild/moderate CDI[a]: $8,8556.13 Severe CDI[b]: $41,810.36 Mean hospital LOS mild/moderate CDI: 16.4 days Mean hospital LOS severe CDI: 22 days [a] 32% of mild/moderate CDI patients were assumed to require hospitalisation: [b] 100% of severe CDI patients were assumed to be hospitalised.
Financial estimates		

Component	Submission considered in November 2017 *PBAC recommendations in italics*	Current resubmission
Uptake rate	Year 1: 20% Year 2: 30% Year 3: 40% Year 4: 50% Year 5: 50% Year 6: 50%	Year 1: 40% Year 2: 50% Year 3: 60% Year 4: 70% Year 5: 80% Year 6: 80%
Eligible patient population	Outpatient population. Assumed 10% of patients will use metronidazole + bezlotoxumab (based on assumption that 90% of eligible patient population used vancomycin + bezlotoxumab).	High risk patient population (inclusive of inpatient and outpatients). To align with the requested restriction, the patient population estimate assumed 95% with positive Toxin B test. Adjusted for 42.6% metronidazole usage (based on MODIFY trials, and excluded fidaxomicin use).
Administration cost	Not included	MBS 14245 intravenous infusion of PBS Section 100 agent $97.95

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 aged 65 years or greater, are immunocompromised, have a history of CDIs, have had a clinically severe episode, or have a hypervirulent CDI ribotype.

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 resubmission provided a revised clinical management algorithm reflecting the listing for high risk patients. If bezlotoxumab is to be listed as proposed, then patients at high risk of recurrence will be administered bezlotoxumab as add-on to antibiotic therapy for both initial and recurrent CDIs (non-severe and severe episodes). The resubmission also indicated that bezlotoxumab would mostly be administered alongside vancomycin, an assumption that was carried through the modelled economic evaluation and financial estimates.

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. The PBAC recalled that at the November 2017 meeting it considered this to be appropriate (Paragraph 5.1; Bezlotoxumab November 2017 Public Summary Document (PSD)).

However, the PBAC 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.

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 two head-to-head randomised trials comparing bezlotoxumab to placebo: MODIFY I and MODIFY II. The main clinical trial reports and publications reported data for the total trial population (with patients at low and high risk of CDI recurrence). A manuscript by Gerding *et. al.* 2018[2] (now published online) presented data on the subgroup of patients with at least one risk factor for CDI recurrence (defined as: age ≥65 years, one or more episodes of CDI within the prior 6 months, immunocompromised, clinically severe CDI or having a hypervirulent strain of infection (ribotypes 027, 078 or 244)).

6.4 The dose of bezlotoxumab administered in the trials was 10mg/kg as a single infusion. Bezlotoxumab was administered alongside SoC oral antibiotics in the trials. 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. 42.6%, 52.9% and 4.6% of high risk patients 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

[2] Gerding *et. al.*, Bezlotoxumab for prevention of recurrent C. difficile infection in patients at increased risk for recurrence. Clinical Infectious Diseases, 2018, Publication In Press

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).

6.6 The resubmission argued that CDI recurrence was the most relevant measure of efficacy because: i) bezlotoxumab has no impact on initial clinical cure; and, ii) exclusion of patients not achieving initial cure occurred equally for both arms and as such the relative risk was not biased. However, using recurrence rate was likely to overestimate the true benefit of bezlotoxumab, as patients who do not obtain clinical cure from their index CDI episode would not be able to relapse, but would have received bezlotoxumab regardless. Both the EMA and the FDA considered that global cure would be a more interpretable clinical endpoint. Global cure was also considered to maintain the initial randomisation of the trial, whereas the population evaluated only for recurrence was no longer randomised i.e. patients who did not achieve an initial cure were no longer included in the recurrence analysis (Johnson *et. al.* 2012).

Table 3: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
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 Clostridium difficile toxin A), MK-3067 (Human Monoclonal Antibody to *C. difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *C. difficile* toxin A and toxin B) in Patient Receiving Antibiotic Therapy for *C. difficile* Infection (MODIFY I).	09/10/2015
	Wilcox et al., Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection.	New England Journal of Medicine 2017; 376(4):305-317
	Kelly CP, Gerding DN, Rahav G, The monoclonal antibody, bezlotoxumab targeting *C. Difficile* toxin B shows efficacy in preventing recurrent *C. Difficile* infection (CDI) in patients at high risk of recurrence or of CDI-related adverse outcomes (Abstract)	Digestive Disease Week 2016, San Diego, CA, May 21-24, 2016
	Prabhu VS, Cornely OA, Golan Y, Dubberke ER, Heimann SM, Hanson ME, Liao J, Pedley A, Dorr MB, Marcella S, Thirty-Day Readmissions in Hospitalized Patients Who Received Bezlotoxumab with Antibacterial Drug Treatment for Clostridium difficile Infection	Clinical Infectious Diseases, 1 October 2017, 65(7):1218-1221
	Zar FA, In C difficile infection, adding IV bezlotoxumab to standard antibiotics reduced recurrence at 12 weeks	Annals of Internal Medicine, 16 May 2017, 166(10):JC53
	Yacyshyn B, Rahav G, Kao DH, Ellison M, Pedley A, Eves K, Hanson ME, Guris D, Dorr MB, Efficacy of bezlotoxumab in patients with recurrent clostridium difficile infection (CDI): Pooled analysis of data from the modify trials	Gastroenterology, 2017, 152(5 Supplement 1):S343

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
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 Clostridium difficile toxin B), and MK3415A (Human Monoclonal Antibodies to Clostridium difficile toxin A and B) in Patients Receiving Antibiotic Therapy for Clostridium difficile Infection (MODIFY II)	02/11/2015
	Wilcox et al., Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection.	New England Journal of Medicine 2017; 376:4 (305-317)
	Hust M; Fuhrer V Development of neutralizing human antibodies against Clostridium difficile toxins (Abstract)	68th Annual Meeting of the German Society for Hygiene and Microbiology, DGHM 2016, Ulm, Germany, September 11-14, 2017
	Kelly CP; Gerding DN; Rahav G, The monoclonal antibody, bezlotoxumab targeting *C. Difficile* toxin B shows efficacy in preventing recurrent *C. Difficile* infection (CDI) in patients at high risk of recurrence or of CDI-related adverse outcomes (Abstract)	Digestive Disease Week 2016, San Diego, CA, May 21-24, 2016
	Prabhu VS, Cornely OA, Golan Y, Dubberke ER, Heimann SM, Hanson ME, Liao J, Pedley A, Dorr MB, Marcella S, Thirty-Day Readmissions in Hospitalized Patients Who Received Bezlotoxumab with Antibacterial Drug Treatment for Clostridium difficile Infection	Clinical Infectious Diseases, 1 October 2017, 65(7):1218-1221
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Shaded areas indicate data previously seen by the PBAC
Source: Appendix 3 of the submission

6.7 The PBAC previously considered repeat dosing was likely in clinical practice, however as repeat dosing was not tested in the trials, the efficacy of bezlotoxumab re-administration in patients who experience another recurrence was unknown. The resubmission maintained that the efficacy of bezlotoxumab repeat dosing would be expected to be the same as the initial dosing, based on a significant reduction in recurrence in patients with prior CDIs compared to placebo. The resubmission's reasoning was considered poor; prior CDI is a risk factor for CDI recurrence, however as no patient had prior bezlotoxumab in the trials; it was uncertain how this group of patients could inform efficacy of bezlotoxumab in repeat dosing.

Comparative effectiveness

6.8 Main efficacy outcomes for the MODIFY I and MODIFY II trial high risk populations are summarised in Table 4 and Figure 1 below. The resubmission maintained the

minimal clinically important difference (MCID) from the previous submission, which was the reduction in recurrence of 8-9%. It clarified that this was within the trial period of 12 weeks. The proposed MCID for the total trial population was also assumed for the high risk patient population.

Table 4: CDI Recurrence and Global cure rates at 12 weeks in the high risk^ subpopulation (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				
All participant	129/781 (16.5)	206/773 (26.6)	**-10.0 (-14.0, -6.0)^**	**0.62 (0.51,0.75)**
Overall (≥1 of below risk factor[c])	100/592 (16.9)	174[d]/583 (29.8)	**-12.8 (-17.6, -8.0)**	**0.57 (0.46, 0.71)**
- 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)
027 strain	21/89 (23.6)	34/100 (34.0)	-10.4 (-23.0,2.6)	0.69 (0.44, 1.09)
≥2 previous CDI episodes ever	29/100 (29.0)	53/126 (42.1)	**-13.1 (-25.1,-0.4)**	**0.69 (0.47, 0.99)**
No risk factor	29/189 (15.3)	32/190 (16.8)	-1.5 (-9.0, 6.0)	0.91 (0.58, 1.44)
Used in model: Age ≥65 years or CDI history in the past 6 months or immunocompromised or severe CDI (Zar score≥2)[b]	[redacted]	[redacted]	[redacted]	[redacted]
CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks, stratified by risk factors				
All participant	129/625 (20.6)	206/621 (33.2)	**-12.2 (-17.1, -7.4)^**	**0.62 (0.51, 0.75)**
Overall (≥1 of below risk factor[c])	100/471 (21.2)	174/468 (37.2)	**-15.9 (-21.6, -10.2)**	**0.57 (0.46, 0.70)**
- 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)
No risk factors*	29/154 (18.8)	32/153 (20.9)	-2.1 (-11.1, 6.9)	0.90 (0.58, 1.41)
1 risk factor*	40/234 (17.1)	70/224 (31.3)	**-14.2 (-21.9, -6.4)**	**0.55 (0.39, 0.77)**
2 risk factors*	46/171 (26.9)	69/168 (41.1)	**-14.2 (-24.0, -4.1)**	**0.65 (0.48, 0.89)**
≥3 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				
All participant	496/781 (63.5)	415/773 (53.7)	**9.7 (4.8, 14.5)^**	**1.18 (1.09, 1.29)**
Overall (≥1 of below risk factor[c])	[redacted]	[redacted]	[redacted]	[redacted]
- Age ≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
- ≥1 CDI episode in past 6 months	[redacted]	[redacted]	[redacted]	[redacted]
- Immunocompromised	[redacted]	[redacted]	[redacted]	[redacted]
- Severe CDI; Zar score ≥2	[redacted]	[redacted]	[redacted]	[redacted]
- 027, 078 or 244 strain	[redacted]	[redacted]	[redacted]	[redacted]
027 strain	[redacted]	[redacted]	[redacted]	[redacted]
≥2 previous CDI episodes ever	[redacted]	[redacted]	[redacted]	[redacted]
No risk factor	[redacted]	[redacted]	[redacted]	[redacted]

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

^ Adjusted for stratification factors of hospitalisation status and standard of care therapy.

* 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

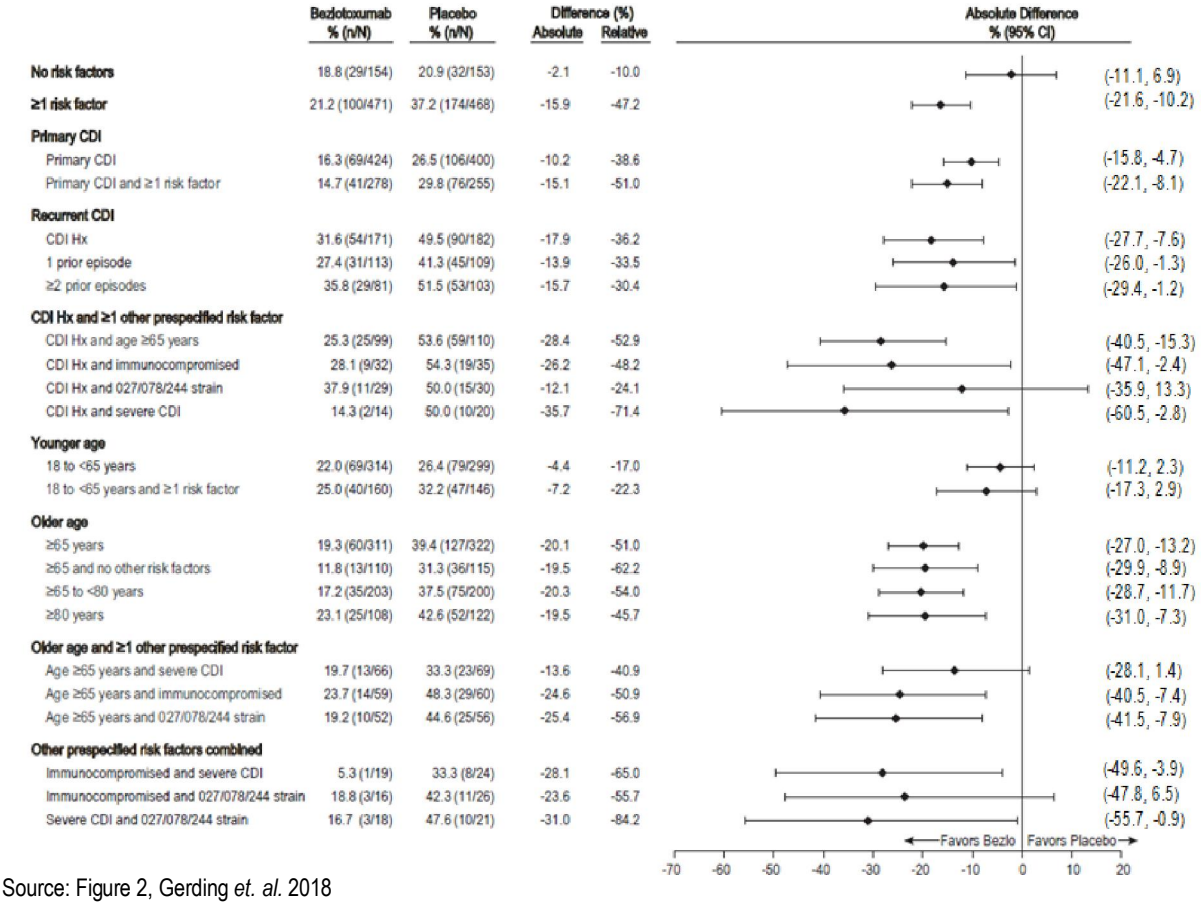
[b] Although hypervirulent strains was a risk factor for CDI recurrence in the MODIFY trials, it was not included as a risk factor to define patients at high risk of recurrence in the economic evaluation due to low prevalence of ribotype 027 strain in Australia.

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

[d] based on the publication Gerding *et. al.* 2018, Figure 2.

Source: Constructed during the evaluation from Tables 2-32-34, pp74-77 of the resubmission. Table 2.2-1, p7 of Appendix 7 of the resubmission and Gerding *et. al.* 2018 (for the high risk group).

Figure 1: CDI recurrence in patients who attained clinical cure, by risk factors



Source: Figure 2, Gerding *et. al.* 2018

6.9 There were fewer CDI recurrences at Week 12 in patients treated with bezlotoxumab versus placebo in the high risk population (RD (95%CI): -12.8% (95%CI: -17.6 to -8.0)), slightly larger than the observed difference in the overall trial population (RD (95%CI): -10.0% (-14.0, -6.0)). Although the upper 95%CI (-8%) passed the lower limit of the nominated MCID of 8-9% reduction in recurrence, it would fail the larger MCID of -9%.

6.10 When considering the outcome of CDI recurrence in the subgroup of patients who attained clinical cure of initial episode, the risk difference for bezlotoxumab and placebo was also larger in the high risk population (RD (95%CI): -15.9% (-21.6, -10.2)) compared to the overall trial population including patients with no risk factors (RD (95%CI): -12.2% (-17.1, -7.4)). This was also observed for the outcome of global cure where a larger benefit was estimated for bezlotoxumab in the high risk population versus the overall trial population (RD (95%CI): [redacted]% ([redacted], [redacted]) versus 9.7% (4.8, 14.5)).

6.11 Among patients with no pre-defined risk factors for CDI recurrence, recurrence rate did not differ between those treated with bezlotoxumab and placebo. The magnitude of treatment effect also varied depending on both the number and type

of risk factors that patients had. In the manuscript by Gerding *et. al.* (2018), the difference in recurrence rates between bezlotoxumab and placebo in those who attained clinical cure of initial episode was larger in patients with prior history of CDI and severe CDI (RD (95%CI): -35.7% (-60.5, -2.8)) compared to the overall high risk (≥1 risk factor) population (RD (95%CI): -15.9% (-21.6, -10.2)). Patients with ≥3 risk factors (RD (95%CI): -24.8 (-39.1, -9.3)) were also more likely to benefit from bezlotoxumab compared to those with only one or two risk factors (RD (95%CI): -14.2% (-21.9, -6.4) and -14.2% (-24.0, -4.1) respectively).

6.12 In November 2017, the PBAC noted that subgroup analyses based on risk factor resulted in risk of recurrence with upper 95%CIs that crossed over the pre-specified MCID (history of CDI in the past 6 months, immunocompromised or severe CDI) or were not statistically significant (hypervirulent ribotype). The PBAC 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 6.14, Bezlotoxumab November 2017 PSD). This remained unchanged in this resubmission.

6.13 True CDI recurrence was also likely underestimated since those who did not achieve clinical cure were considered "successes". This was evidenced in the higher CDI recurrence rates for the subgroup of patients who attained clinical cure (i.e. approximately 80% of the patients with ≥1 risk factor achieved clinical cure; the denominator was reduced by 20% while the numerator remained the same). Nonetheless, as clinical cure rates across the trial arms were similar, the results comparing bezlotoxumab and placebo in terms CDI recurrence and global cure were similar.

6.14 The variation in risk difference by risk factors directly impacts the applicability of the MODIFY I and II trials to the PBS population. If the breakdown of risk profiles (number and type) should differ on the PBS compared to those observed in the MODIFY I and II high risk populations then the likely benefits will also differ.

6.15 No results for the high risk patients were reported in the resubmission beyond 12 weeks. As with the previous submission, efficacy beyond 12 weeks for the overall trial population was informed by results of the MODIFY II extension study, which reported results for a further 9 months for a total of 293 patients, with 99 patients treated with bezlotoxumab and 83 patients treated with placebo (112 patients were treated with a combination of bezlotoxumab and actoxumab; these results have not been included below).

Comparative harms

6.16 Safety outcome data presented in the resubmission were the same as presented in the November 2017 submission. No new safety data specific to the high risk population were presented in the resubmission. During the evaluation, limited safety data on 30-day and 90-day mortality were extracted from Gerding *et. al.* 2018.

Consistent with the overall trial population, there were no statistically significant differences in mortality between high risk patients treated with bezlotoxumab and placebo.

6.17 The ESC considered that the safety of bezlotoxumab in the high risk group of patients may differ from the total population. The ESC also noted that there was a higher incidence of heart failure in bezlotoxumab treated patients compared to placebo treated patients in MODIFY I and II 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. The PBAC noted that the pre-PBAC response presented a summary of adverse event data for high risk patients, which showed similar event rates between the treatment and placebo group.

6.18 As previously reported, 10% (81 out of 786) of patient in the bezlotoxumab arm had experienced an infusion specific adverse event (AE). In addition the resubmission reported (p66) that in the total trial population (n=2579[3]), of the patients who experienced an infusion related AE (n=228) most of the reactions were mild (76%) or moderate (22%) in nature and the majority of reactions resolved within 24 hours of onset. Data was not presented in the resubmission to verify the claim that most reactions resolved within 24 hours. A search of the clinical trial reports indicated while there were fewer AEs (including fewer general disorders and administration site conditions) reported within 24 hours of infusion compared to AEs reported during infusion, no further data was available to permit verification that the reduction in event reporting was due to resolution of AEs. The PBAC recalled that it previously considered that because SoC does not require an infusion, patients treated with bezlotoxumab may suffer additional infusion related adverse events (paragraph 6.30; bezlotoxumab November 2017 PSD).

Benefits/harms

6.19 A summary of the comparative benefits and harms for bezlotoxumab plus SoC versus SoC alone is presented in Table 5 below.

[3] Note this also included patient from actoxumab and actoxumab+bezlotoxumab treatment arms.

Table 5: Summary of comparative benefits and harms for bezlotoxumab and SoC in the trials (total trial populations and subgroup with at least one risk factor^ for CDI recurrence)

Benefits						
CDI recurrence at 12 weeks						
Trial	**Bez + SoC**	**SoC**	**RR (95% CI)**	**Events/100 patients[a]**		**RD (95% CI)**
				Bez + SoC	**SoC**	
MODIFY I (total population)	67/386	109/395	**0.63 (0.48,0.82)**	17.4	27.6	**-10.1 (-15.9,-4.3)**
MODIFY II (total population)	62/395	97/378	**0.61 (0.46,0.81)**	15.7	25.7	**-9.9 (-15.5,-4.3)**
Pooled (total population)	129/781	206/773	**0.62 (0.51,0.75)**	16.5	26.6	**-10.0 (-14.0,-6.0)**
Pooled (≥1 risk factors)	100/592	174/583	**0.57 (0.46, 0.71)***	16.9	29.8	**-12.8 (-17.6, -8.0)***
Global cure at 12 weeks						
MODIFY I (total population)	232/386	218/395	1.09 (0.97,1.23)	60.1	55.2	4.9 (-2.1,11.7)
MODIFY II (total population)	264/395	197/378	**1.28 (1.14,1.45)**	66.8	52.1	**14.6 (7.7,21.4)**
Pooled (total population)	496/781	415/773	**1.18 (1.09,1.29)**	63.5	53.7	**9.7 (4.8,14.5)**
Pooled (≥1 risk factors)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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)						
MODIFY I and II total population (pooled)	81/786 (10)	0/781[b]	**162.0 (21,NA)***	10.3	0	**10.0 (8.3,12.6)***

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

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

[a] At 12 weeks of follow-up for all trials

[b] Comparator in practice is no treatment therefore do not expect any infusion related adverse events

* values calculated during evaluation

Source: Compiled during the evaluation using data from Table 11-1, p206 MODIFY I CSR, Table 11-1, p211 MODIFY II CSR, Table 2.7.3-rcdi: 19, p87 and table 2.7.3-rcdi: 23, p97 CSR RCDI, Tables S5 to S8 of the supplementary Appendix to the published report (Wilcox *et. al.* 2017) and Tables 2-32-34, pp74-77 of the resubmission. Table 2.2-1, p7 of Appendix 7 of the resubmission and Gerding *et. al.* 2018 (for the high risk group).

6.20 On the basis of direct evidence presented by the resubmission, for every 100 high risk patients treated bezlotoxumab plus SoC versus SoC alone:

- Approximately 13 fewer patients would have CDI recurrence (17 vs 30);
- Approximately 12 more patients would achieve global cure (clinical cure of initial CDI episode plus no CDI recurrence) (62 vs 50)

On the basis of direct evidence presented by the resubmission, for every 100 patients treated with bezlotoxumab plus SoC versus SoC alone:

- Approximately 10 more patients would experience an infusion specific adverse event.

Interpretation of clinical evidence

6.21 The resubmission described bezlotoxumab plus SoC antibiotic treatment in patients with CDI as superior in efficacy for prevention of recurrence and non-inferior in safety compared to SoC antibiotics alone. This claim was unchanged from the November 2017 submission.

6.22 The PBAC had previously considered that the claim of superior comparative effectiveness was supported by data, however, the overall benefit remained modest and the clinical significance was unclear, despite limiting the indication to the group at high risk of recurrence .

6.23 The PBAC recalled that it previously considered that the claim of non-inferior comparative safety was not supported by the data when compared to SoC oral antibiotics alone since patients treated with bezlotoxumab infusion will be exposed to infusion AEs (p21, bezlotoxumab November 2017 PSD) and because of the risk of heart failure. The PBAC noted that the resubmission clarified that the infusion-related AEs, which occurred in 10% of patients treated with bezlotoxumab, were mostly mild (76%) or moderate (22%) in nature. Nonetheless, the PBAC considered that these are additional adverse events that would be experienced by patients treated with bezlotoxumab and not with SoC oral antibiotics. Furthermore, the PBAC noted the ESC's advice that while infusion related AEs were mostly mild, all AEs had not been separately analysed for the 'high risk group' and that the prevalence and severity may differ in this group, particularly given the subgroups with a history of heart failure in MODIFY I and II had a higher incidence of acute heart failure and higher mortality when treated with bezlotoxumab than with placebo, and that heart failure increases with age, which is one of the nominated factors for high risk of CDI recurrence.

6.24 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.25 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data and that a claim of inferior safety would be more appropriate.

Economic analysis

6.26 The structure of the modelled economic evaluation remained largely unchanged from the November 2017 submission, however; a number of adjustments were made in this resubmission to address issues raised by the PBAC. Table 6 summarises the key model components in the previous submission and this resubmission.

Table 6: Key components of the economic evaluation including comparison with November 2017 submission

Component	November 2017	Current submission
Type of analysis	Stepped cost-utility analysis	Stepped cost-utility analysis
Patient population	Outpatient population (based on MODIFY I and II trials) • Age at model entry: 56.7 • Proportion of females: 63.3 • Entering with severe CDI: 3.6	High risk population based on MODIFY I and II trial subgroups. High risk was defined by the resubmission as having at least one of the following risk factors: age ≥ 65 or history of CDI in the past 6 months, immunocompromised or severe CDI)^. • Age at model entry: **68.1** • Proportion of females: 55.8% • Entering with severe CDI: 22.7%
Outcomes	Cost per CDI recurrence avoided; cost per life year (LYG) gained; cost per quality adjusted life year (QALY) gained.	Cost per CDI recurrence avoided; cost per life year (LYG) gained; cost per quality adjusted life year (QALY) gained; and number of hospital bed days avoided.
Treatment setting	Outpatients in base case	No longer restricted to outpatients.
Time horizon	10-year time horizon as base case. 5 years and lifetime were tested in sensitivity analysis.	10-year time horizon as base case.
Methods used to generate results	Markov cohort analysis	Markov cohort analysis
Health states	8 main health states: • mild/moderate CDI; • severe CDI; • clinical cure; • clinical failure; • colectomy; • recurrent mild/moderate CDI; • Recurrent severe CDI; and • Death.	7 main health states (removing the colectomy health state) • mild/moderate CDI; • severe CDI; • clinical cure; • clinical failure; • Recurrent CDI mild/moderate • Recurrent severe CDI; and • Death.
Cycle length	15 days in the first year, annual cycle length thereafter; with half cycle corrections to costs and benefits.	30 days in the first year, annual cycle length thereafter; with half cycle corrections to costs and benefits.

Component	November 2017	Current submission
Transition probabilities	Efficacy estimates regarding the probability of CDI recurrence were derived from the MODIFY I and MODIFY II outpatient population adjusted to the 15 day cycle length in the first year of the model. Mortality (up to 180 days) were informed by Olsen (2015): • 180-day all-cause mortality (no recurrences): 25.7% (adjusted to 15-day mortality 0.0245) • 180-day all-cause mortality (recurrences): 36.3% (adjusted to 15-day mortality 0.0391) • Hazard ratio mortality (calibrated): 1.6 Background deaths (after 180 days) were informed by Australian Bureau of Statistics life tables.	Efficacy estimates regarding the probability of CDI recurrence were derived from the MODIFY I and MODIFY II high risk population in an "Ad hoc analysis of MODIFY I and MODIFY II trials. Merck & Co., Inc. data on file". This was an augmented "high risk" group compared to the trial, removing patients whose only risk factor was having a hypervirulent strain of CDI. No data were provided in the resubmission to permit verification of the estimated treatment effect for bezlotoxumab versus placebo. Mortality remained a key driver of cost effectiveness, despite no difference in mortality between bezlotoxumab and placebo treated patients in the MODIFY trials. Mortality (up to 180 days) were informed by the literature (with calibration step removed): • 30-day all-cause mortality (no recurrences) were informed by Huber *et. al.* 2014, an Australian publication: 3.6% • 30-day all-cause mortality (recurrences) was estimated using the hazard ratio for mortality of 1.33 (from Olsen 2015) to be 4.79%. Background deaths (after 180 days) were informed by Australian Bureau of Statistics life tables.
Costs associated with bezlotoxumab	- Only one dose of bezlotoxumab was permitted in the model. - Bezlotoxumab + administration: $[redacted] - Assumed 10% of patients (weight>100kg) will need 2 vials	- Despite the requested restrictions permitting re-dosing after 90 days, patients in the model were only permitted one dose of bezlotoxumab. - Bezlotoxumab + administration: $[redacted] (reflecting a [redacted]% price reduction plus specialist visit for infusion specific AEs in 10% of the patients). - Assumed 7.3% of patients (weight>100kg) will need 2 vials.
Resource costs	- Cost per mild/moderate CDI recurrence: $4443.69#, this included cost of vancomycin, GP and Specialist visits and two pathology tests for CDI and 32%# of recurrences were assumed to require hospital admissions at $12,563 per episode. - Cost per severe CDI recurrence: $30,890.70 (assumed 100% of patients will be hospitalised and that 0.7% of those with severe CDI will require colectomy at cost of $6,539 per episode).	- Cost per mild/moderate CDI recurrence: $8556.13 this included cost of vancomycin, GP and specialist visits and two pathology tests for CDI and 32% of recurrences were assumed to require hospital admissions at $25,470.23 per episode (inflating the NHCDC AR-DRG cost weight for T64B by a factor of 2.03). - Cost per severe CDI recurrence: $41,810.36 (assumed 100% of patients will be hospitalised, inflating the AR-DRG T64A costs by a factor of 1.35). - Mean hospital LOS mild/moderate CDI: 16.4 days - Mean hospital LOS severe CDI: 22 days
Software package	Microsoft® Excel 2010	Microsoft® Excel 2010

Abbreviations: CDI=*clostridium difficile* infection; AE=adverse event; SoC=standard of care; LOS=length of stay

Shaded areas indicate data previously seen by the PBAC.

^ Redefined high risk group removing patients with hypervirulent strain (0.27, 0.78, 244 ribotypes).

Note a transcription error was detected in the November 2017 model, the proportion of mild/moderate CDI patients requiring hospitalisation was incorrectly calculated to be 41.7%, once transcription error was corrected the proportion of mild/moderate CDI patients requiring hospitalisation was 32%, with an associated cost of $4443.69 (the submission's cost was: $5,667.72).

Source: Table 3-2, p87 of the resubmission.

6.27 The data used to inform the modelled economic evaluation was based on an *ad hoc* analysis conducted by the sponsor, which removed patients whose only risk factor for recurrence was being infected with a hypervirulent strain of CDI (ribotypes 0.27, 078 or 244), on the basis that the 027 ribotype has low prevalence in Australia. . However, ribotype 244 is reasonably common in Australia. The data and results from the *ad hoc* analysis were not provided with the resubmission for verification Despite these shortcomings, as the number of patients excluded from the *ad hoc* analysis was small (n=[redacted]; [redacted]% 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.

6.28 All patients enter the model with a current CDI, either mild/moderate or severe (based on the MODIFY I and II trial proportions). The model assumed a 30-day cycle length for the first year and annual cycles thereafter. In the first cycle (Days 0-30), patients with mild/moderate or severe CDI can transition into one of the following health states: clinical cure, clinical failure or death.

6.29 Patients who transitioned to clinical cure can experience recurrent CDI in the next cycle based on the 30-day probabilities (estimated from MODIFY I and MODIFY II data). Only patients in clinical cure can experience CDI recurrence within 30 days (1 cycle). Those who do not have a CDI recurrence 1 cycle post attaining clinical cure were assumed to not have any CDI recurrence for the rest of the model (base case time horizon 10 years). The MODIFY II extension study provided follow-up data for only 12 months.

6.30 A mortality difference was assumed between those with and those without CDI recurrence. The 30-day mortality without CDI recurrence (3.6%) was sourced from Huber *et. al.* 2014 then the mortality rate for patients with recurrence were estimated by multiplying this value by the mortality hazard ratio (HR) reported by Olsen *et. al.* 2015 (1.33). These mortality rates were applied for the first 180 days (6 cycles) of the model. Mortality after 180 days was based on the Australian Bureau of Statistics life tables.

6.31 All patients who do not die or transition to clinical cure after 1 cycle transition to clinical failure health state. Patients in clinical failure were assumed to have a health state utility the same as for mild/moderate CDI (0.880) for the cycle irrespective of whether their initial CDI was mild/moderate or severe. Due to a lack of data to inform inputs, patients in clinical failure were assumed to have the same risk of death as patients in clinical cure, and transition after 1 cycle to a post clinical failure state where the patient could not experience CDI recurrence and was assumed to have a health state utility of 1.

6.32 Health state utilities were calculated based on the patient's health state multiplied by the corresponding quality of life based on the patient's age and gender, which were based on a population self-reported health using the EQ-5D instrument(Szende 2014).

6.33 Patients with CDI recurrence can have either mild/moderate or severe CDI. Similar to initial CDI episodes, patients may then transition to clinical cure, clinical failure or death. Patients who achieved clinical cure from the first CDI recurrence may experience further CDI recurrence within 30 days (1 cycle) of the recurrent episode. The recurrence rate for the first 30 days of the model was based on the 84-day probability of recurrence from the MODIFY trials (which favours bezlotoxumab as benefits are accrued earlier). The recurrence rate for 2nd and 3rd CDI recurrence was the same for both treatment arms and was assumed to occur at a greater rate than observed in the MODIFY I and MODIFY II of 45%.

6.34 A total of three CDI recurrences were permitted in the model, after which patients cannot experience any more CDI recurrences. Due to model set up, all recurrences occurred within the first 150 days in the model. The remainder of the model time horizon (3496 days) was not informed by outcomes from the MODIFY I and MODIFY II trials.

6.35 Based on PBAC feedback from the November 2017 submission, the updated modelled economic evaluation appropriately assumed that 10% of patients receiving bezlotoxumab (as per trial results) will experience an infusion related event with an associated cost of one specialist visit.

6.36 Key drivers of the economic evaluation are summarised in Table 7.

Table 7: Key drivers of the model

Description	Method/Value	Impact on ICER
CDI recurrence rate for SoC	The 30-day first CDI recurrence rate for SoC and bezlotoxumab were informed by results of the MODIFY trials (resubmission augmented high risk population. There is potential for recurrence rate for SoC in Australia to be lower than reported in the trials (29.8%). The model was very sensitive to this assumption. Assuming 30-day first CDI recurrence rate for SoC to be 17.5% (based on Foster *et. al.* 2017 and assuming constant CDI over time) and RR of 0.56 for bezlotoxumab versus SoC (from the trials) estimating a first CDI recurrence rate for bezlotoxumab of 9.8% the ICER increased to over $200K/QALY.	Very High Favoured bezlotoxumab
Baseline Mortality	The model was very sensitive to the assumed all-cause mortality for those with CDI recurrence and without. These were informed by the literature as the trials did not find any difference in death rates. 180-day mortality following non-recurrent CDI was based on 30-day mortality in an aggregate CDI population (i.e. including patients w/ and w/o recurrence). Despite only being applied for a very short time in the model (180 days), mortality was critical to the ICER. Assuming lower mortality values, e.g. a lower hazard ratio for mortality of recurrent CDI versus no recurrence (i.e. using the lower 95%CI reported in Olsen *et. al.* 2015 of 1.12 rather than the 1.33 assumed in the base case) and assuming a lower 30-day mortality rate for non-recurrent CDI (2.5% based on the alternate Australian value from Foster *et. al.* 2014 instead of the 3.6% assumed in the base case) independently and jointly lead to ICER in excess of $105K/QALY – 200K/QALY.	High Favoured bezlotoxumab
CDI recurrence rate for SoC	The 30-day first CDI recurrence rate for SoC and bezlotoxumab were informed by results of the MODIFY trials (resubmission augmented high risk population. There is potential for recurrence rate for SoC in Australia to be lower than reported in the trials (29.8%). The model was very sensitive to this assumption. Assuming 30-day first CDI recurrence rate for SoC to be 17.5% (based on Foster *et. al.* 2017 and assuming constant CDI over time) and RR of 0.56 for bezlotoxumab versus SoC (from the trials) estimating a first CDI recurrence rate for bezlotoxumab of 9.8% the ICER increased to over $200K/QALY.	Very High Favoured bezlotoxumab
Mortality hazard ratio	A hazard ratio was applied to the (high) baseline mortality rates, which was taken from an observational study, in which the authors acknowledged two key sources of bias that likely resulted in the overestimation of the true hazard ratio.	High Favoured bezlotoxumab
Repeat recurrences	The model structure allows for up to 3 recurrences, with high probabilities of recurrence (45% experience a 2nd recurrence and 45% of those experiencing a 3rd recurrence experience a third recurrence)	High Favoured bezlotoxumab
Hospitalisation cost for CDI	Hospitalisation cost for severe and mild/moderate CDI in the model were inflated above NHCDC National cost weights for AR-DRGs T64A and T64B (respectively) using the reported longer hospital LOS reported in a UK based study (Wilcox *et. al.* 2017b). This was inappropriate as average LOS reported in NHCDC National cost weights were already generous in length, particularly for mild/moderate CDI. The LOS for AR-DRG T64B from the NHCDC National cost weights included an average LOS of 8.09 days, which was likely an overestimate for patients with mild/moderate CDI (sources suggest diarrhoea resolution was common by Day 6 and CDI clearance within 6-10 days from onset), therefore a further upward adjustment by a factor of 2.03 to 16.4 days was likely to overestimate cost of admissions for mild/moderate CDI. Removing the inflation factors, the ICER increased to $45,000/QALY - $75,000/QALY (a 75% increase from base case).	High Favoured bezlotoxumab

Abbreviations: CDI=*clostridium difficile* infection; SoC=standard of care antibiotics; QALY=quality adjusted life years; LOS=length of stay
Source: Constructed during the evaluation using values presented in Table 3-21, p121 of the resubmission

6.37 Table 8 summarises the results of the stepped economic evaluation for the high risk patient population.

Table 8: Results of the stepped economic evaluation in the resubmission

Step and component	Bezlotoxumab + SoC	SoC only	Increment
Step 1: Used high risk subpopulation from MODIFY I and MODIFY II			
Costs	$	$0	$
Outcomes (CDI recurrence rate)	16.7%	29.7%	13%
Cost per CDI recurrence avoided			$
Step 2: Used Markov model to determine life years			
Costs	$	$	$
Outcomes (life years)	5.7306	5.6935	0.0371
Cost per life year gained			$ ^
Step 3: Applied utility weights to Markov model to determine QALYs			
Costs	$	$	$
QALYs	4.6961	4.6637	0.0324
Cost per QALY gained (base case)			**$**

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

^ The half-cycle adjustment was not properly applied across the different cycle lengths between the last 30-day cycle in year 1 and year 2 (annual cycle length) resulting in a missing 0.47 life-year. Correcting for the half-cycle adjustment resulted in incremental cost per life year $15,000 – $45,000 and ICER of $15,000/QALY – $45,000/QALY.

Source: Table 3-17, p115 and Bezlotoxumab Sec 3 Workbook of the resubmission

The redacted table shows the base case ICER in the range of $15,000/QALY - $45,000/QALY.

6.38 The main drivers of the modelled economic evaluation were mortality, CDI recurrence and hospitalisation costs. Concerns with inputs used in the resubmission included:

- Although the assumed mortality rates in the model were reduced compared to the November 2017 submission, the mortality rate for patients with recurrent CDI may also be lower than assumed in the model, with one reference suggesting mortality was 2.5% in hospitalised patients with CDI (compared to the 3.6% used in the submission). Assuming more severe patients are hospitalised, then mortality rate in the community could be even lower (particularly for patients with mild/moderate CDI).
    - The Huber paper reporting the 3.6% mortality rate was not provided with the submission. ESC noted that it appears that the reported 3.6% reflects aggregate mortality (i.e. with and without recurrence), implying mortality in non-recurrent cases would be lower, somewhere between 0.032 and 0.035, depending on assumptions on proportion of first CDI cases and the mortality HR for recurrent vs. first CDIs.
    - The PSCR noted that the Foster (2014) paper reporting a mortality rate of 2.5% was calculated from two hospitals in Western Australia, where 2 patients died out of a total of 80 patients in the trial and that 90-day mortality was 16.3% (equivalent to 5.8% 30-day probability). The PSCR also cited other studies reporting higher 30-day mortality rates, including a

systematic review of the evidence regarding mortality and CDI by Mitchell (2012), which found the 30-day mortality rates to range between 9% and 38%. This PSCR argued that this study, which included over 20,000 patients, should be considered a higher level of evidence than the paper by Foster (2014). The ESC noted that a slightly reduced baseline mortality probability of 0.34 may be reasonable, but considered that mortality rates in Australia were uncertain and that the reported 2.5% in hospitalised patients was relevant to the submission.

- The PBAC noted that the pre-PBAC response referred to a study by Chen *et. al.* 2017 which reported in-hospital mortality rate for CDI admissions as 7.3%. The PBAC noted that this study included hospitalised CDI only, and considered that this would exclude the less severe patients and therefore the mortality rate for all CDI cases was likely lower.
- The PBAC also considered that not all deaths in patients admitted for CDI could be attributed to CDI.

Taken together, the PBAC considered that a more conservative estimate would be appropriate.

- The ESC noted that the HR point estimate (1.33) for mortality applied to patients with recurrent CDI compared to non-recurrent CDI in the model was likely to be an overestimate. The observational study from which the HR was derived acknowledged the following limitations that are likely to have overestimated the mortality effect of recurrent CDI:
  - they were more likely to miss less severe recurrent cases;
  - the lack of data on *C. difficile* strain is important because the 027/BI/NAP1 strain has been associated with both increased risk of CDI recurrence and mortality and is therefore a potential confounder.

  The PBAC did not agree with the pre-PBAC response, which claimed that this approach was conservative.
- The MODIFY trials noted no evidence of mortality benefit associated with bezlotoxumab compared to SoC. The pre-PBAC response reiterated that these trials were not powered to detect a difference in mortality. The PBAC acknowledged that while this does not exclude the possibility that bezlotoxumab may confer a mortality benefit, a lack of evidence that bezlotoxumab does confer a mortality benefit is further justification for a conservative approach to estimating mortality.
- The probability of first recurrence for the SoC group in the trial and the modelled economic evaluation was higher than estimated using cross sectional Australian data (17.5% assuming constant CDI over time compared to 30% in the model). A

lower baseline recurrence rate means the absolute benefit of bezlotoxumab in the Australian population may be lower, making it less likely to be cost effective. The PSCR noted that the lower first recurrence rate is based on 14 of 80 patients recurring (data derived from patients from two hospitals in Western Australia in 2014). The pre-PBAC response further argued that as these data are not specific to high risk patients and excludes outpatients that it may be an underestimate. The PBAC considered that due to the considerable uncertainty, a more conservative approach was warranted.

- The ESC noted that re-recurrence probabilities used in the submission are taken from the following figure from a general review of CDI (Kelly, 2012) and that the relevance and validity of the five referenced studies and how this figure was assembled from those five studies is not clear.

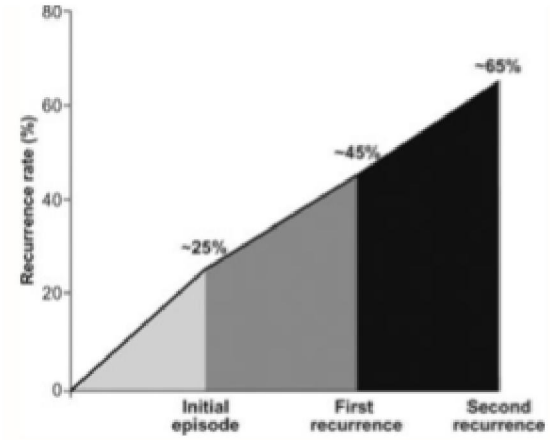


FIG. 2. Frequency of recurrent *Clostridium difficile* infection (CDI) following an initial episode and first and second recurrence [4,12,13,28,29].

Source: Kelly, C.P. (2012). Can we identify patients at high risk of recurrent *Clostridium difficile* infection? Clin Microbiol Infect 2012; 18 (Suppl. 6): 21–27v (p.23)

- The revised hospital cost of mild/moderate and severe CDI following adjustment by a greater length of stay (LOS) reported by Wilcox et. al. 2017b was also likely inappropriate as it increased the incremental healthcare cost and did not appear to reflect LOS reported in the literature, particularly for mild/moderate CDI. This likely biased the ICER in favour of bezlotoxumab.
    - The PSCR stated that "the revised length of stay estimates used in the resubmission were based on a recent publication by Wilcox (2017) specifically relating to patients with recurrent CDI" (in the United Kingdom); and that "compared to matched inpatient controls with an initial CDI episode only, the mean length of stay was 1.4 times longer for patients with severe rCDI and 2.0 times longer for mild/moderate rCDI".
    - The ESC noted that the Wilcox study (which was not provided by the

sponsor), matched patients based on "an rCDI case according to date of first positive CD toxin test (+12 weeks), age group (75/75 years) and gender". The ESC considered that there was a potential for many unobserved confounders and noted that significant differences in comorbidities were reported.

- The PBAC agreed with the ESC that it was not appropriate to multiply costs by a ratio of LOS as inpatient costs are frontloaded. The ESC also noted that Wilcox 2017 reports that "median total management cost (post-index) was £7539 and £6294 for recurrent CDI and first CDI" (a ratio of 1.2). Overall, the upward adjustment of the AR-DRG costs for recurrent CDI is not supported.

- The resubmission did not permit re-dosing of bezlotoxumab in patients who experience a recurrence beyond 90 days, which did not reflect the listing requested. Given patients in the model were followed for 10 years any re-dosing of bezlotoxumab of modelled patients would directly impact both comparative cost and effectiveness of the bezlotoxumab versus placebo therapy.

6.39 In multivariate analyses, when a combination of these factors were tested in sensitivity analyses; all estimated ICERs exceeded $105,000 - $200,000 per QALY (see Table 9).

6.40 Given the uncertain assumptions for mortality due to CDI recurrence, CDI recurrence rate in Australian clinical setting and hospitalisation costs, the base case ICER was considered uncertain and likely an underestimate. The ESC considered that a multivariate sensitivity analysis adjusting the SoC and bezlotoxumab recurrence probabilities, baseline 30-day mortality probability, the mortality HR, hospital costs and re-recurrence probabilities may be the most realistic estimate of the ICER. With a baseline mortality probability of 0.034 the ICER is more than $200,000/QALY and with a baseline mortality probability of 0.025 the ICER is more than $200,000/QALY. The PBAC considered that the most informative analysis within the provided model structure was to apply the following parameters: 10 year time horizon, HR for mortality due to CDI 1.12, 2.5% mortality without CDI recurrence, lower recurrence rates for SoC (17.5%) and bezlotoxumab (9.8%), hospitalisation costs as per AR-DRG. The PBAC noted that a sensitivity analysis applying these parameters resulted in an ICER per QALY of more than $200,000.

Table 9: Results of univariate sensitivity analyses

	Incremental costs	Incremental QALY	Cost per QALY
Multivariate analysis			
- Base case: 10 years, single dose, mild/moderate and severe CDI	$[redacted]	0.0324	$[redacted]
- Assume 5 year time horizon, repeat dose of bezlotoxumab (cost implications only)e	$[redacted]	0.0189	$[redacted]
- Assume mild/moderate or severe CDI: 0.42, clinical failure: 0.42, post CDI and post-clinical failure: 0.8 (Wilcox *et. al.* 2017b) plus HR for recurrent CDI versus no recurrence=1	$[redacted]	0.0059	$[redacted]
- Assume 10 year time horizon, HR for mortality due to CDI recurrence =1.12, a lower 2.5% mortality for CDI without recurrence (from Foster *et. al.* 2014), lower recurrence rate for SoC (Foster *et. al.* 2014) of 17.5%, and a recurrence rate for bezlotoxumab of 9.8% (estimated using the RR of 0.56 from the resubmission's ad-hoc analysis).	$[redacted]	0.0059	$[redacted]
- Assume 10 year time horizon, HR for mortality due to CDI recurrence =1.12, a lower 2.5% mortality for CDI without recurrence (from Foster *et. al.* 2014), lower recurrence rate for SoC (Foster *et. al.* 2014) of 17.5%, and a recurrence rate for bezlotoxumab of 9.8% (estimated using the RR of 0.56 from the resubmission's ad-hoc analysis), hospitalisation cost as per NHCDC national cost weights for AR-DRG, severe CDI T64A $31,695.78; mild/moderate CDI T64B $4,493.02.	$[redacted]	0.0059	$[redacted]
- Assume 10 year time horizon, - Baseline 30-day mortality probability of 0.034 - HR for mortality due to CDI recurrence =1.12, - lower recurrence rate for SoC (Foster *et. al.* 2014) of 17.5% and 9.8% for bezlotoxumab of 9.8% - hospitalisation cost as per NHCDC national cost weights for AR-DRG - re-recurrence probabilities assumed equal to recurrence rate (17.5% as for placebo group since no re-dosing of bezlotoxumab in model)	$[redacted]	0.0072	$[redacted]
- same as immediately above but change baseline 30-day mortality probability to 0.025 (as per Foster *et. al.* 2014).	$[redacted]	0.0057	$[redacted]

The redacted table shows ICERs in the range of $15,000/QALY – more than $200,000/QALY.

Drug cost/patient/treatment $[redacted]

6.41 The average cost of bezlotoxumab was assumed to be $[redacted], based on the DPMQ (private hospital) for 1 vial of 1,000mg and assuming 7.3% of the population will require two vials (weight >100kg); and that patients will only use one dose per course of treatment. The cost for the comparator was $0 as it was assumed that the cost for SoC was unchanged with bezlotoxumab.

Estimated PBS usage & financial implications

6.42 This resubmission was not considered by DUSC; however DUSC had previously considered the November 2017 submission. As with the previous submission, the resubmission took an epidemiological approach to estimate the number of CDI patients eligible for bezlotoxumab treatment. The number of prescriptions required for bezlotoxumab was based on the number of PBS prescriptions for oral vancomycin (for CDI) plus an additional 42.6% use assumed to be use alongside metronidazole in

each year of the financial estimates (using the ratio from the MODIFY trials). Given DUSC had previously noted vancomycin use for CDI in Australia is restricted to pseudomembranous colitis, which only accounts for approximately 10% of CDIs (5.03.DUSC ADV.1 Bezlotoxumab November 2017 PBAC meeting), the submission's approach relying on vancomycin script numbers but not adjusting for higher proportional use of metronidazole underestimated likely bezlotoxumab use on the PBS.

6.43 The financial estimates did not take into account re-dosing with bezlotoxumab for CDI recurrences beyond 90 days of the index infection. The additional health care cost for infusion specific AEs (e.g. one specialist visit was assumed in the modelled economic evaluation) was also omitted in the financial estimates.

6.44 Table 10 summarises the estimated use and financial implications of listing bezlotoxumab.

Table 10: Estimated net cost of bezlotoxumab to the PBS/RPBS

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Projected patient CDI episodes (>18 years)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	Patient episodes with positive toxin B[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	Patients using metronidazole[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Total Toxin B positive episodes treated with either vancomycin or metronidazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Recurrence from previous year in world without bezlotoxumab (assume recurrence rate: 29.8%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	Recurrence from previous year in world with bezlotoxumab	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	- treated with bezlotoxumab (recurrence rate 16.9% x assumed uptake rate for current year)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	- untreated with bezlotoxumab (recurrence rate 29.8%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G	Total recurrence avoided due to bezlotoxumab listing (E-F)	0*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H	Patients eligible to receive bezlotoxumab (D-G)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
I	Assumed bezlotoxumab uptake	40%	50%	60%	70%	80%	80%
J	Bezlotoxumab infusions (H x I)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
K	Bezlotoxumab vials used (assume 7.3% will use 2 vials)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L	PBS/RPBS cost [d]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
M	PBS/RPBS cost (net of patient copayment)[e]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
N	Vancomycin treatments avoided due to bezlotoxumab listing [f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
O	Net PBS/RPBS cost of vancomycin avoided[g]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
P	Net change to PBS/RPBS costs[h]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Q	Net change to MBS costs for bezlotoxumab administration [i]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
R	Net change to government budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: CDI=*Clostridium difficile* infection;

* this is zero since there was no bezlotoxumab in the previous year.

[a] Estimated based on vancomycin prescriptions provided to patients <18 years of age was 1.65%.

[b] Assumed 95% of patient episodes would test positive to toxin B at screening.

[c] Assumed additional 42.6% metronidazole usage (based on MODIFY trials) each year.

[d] Assumed DPMQ $[redacted] per vial of bezlotoxumab (Private hospital)

[e] Assumed average co-payment for bezlotoxumab on the PBS was $17.14 and RPBS was $5.48.

[f] Estimated as the difference between rate of CDI recurrence in patients not treated with bezlotoxumab and treated with bezlotoxumab (29.8%-16.9%) multiplied by the uptake rate and total eligible patients for bezlotoxumab using vancomycin (57.4%).

[g] Assume that 67% of all vancomycin scripts will be 125mg (DPMQ: $230.47) and the remaining 33% will be 250mg (DPMQ: $460.89) and an average co-payment for vancomycin avoided for PBS is $17.60 and RPBS is $6.30.

[h] Net cost of bezlotoxumab minus the cost of vancomycin avoided.

[i] Estimated bezlotoxumab infusions patients (+vancomycin or +metronidazole) multiplied by MBS item 14245 ($97.95).

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

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.45 The total cost to the PBS in the first 6 years of bezlotoxumab listing on the PBS was estimated to be $60 - $100 million (previously $30 - $60 million in the November 2017 submission, a 98% increase). The main changes to the financial estimates between the resubmission and the November 2017 submission were the increase in

the eligible patient population (due to the change in requested restriction) and uptake rate of bezlotoxumab as well as the inclusion of the MBS cost for the administration of bezlotoxumab (MBS item 1245).

6.46 Results of sensitivity analyses around assumed financial parameters (including results of additional sensitivity conducted during the evaluation) are presented in Table 11. All presented sensitivity results below were adjusted in the evaluation to include an additional $97.95 administration cost per bezlotoxumab infusion (MBS item 14245).

Table 11: Sensitivity analyses for the financial estimates updated during the evaluation

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	$	$	$	$	$	$
10% increase in eligible patients	$	$	$	$	$	$
5% increase in annual uptake	$	$	$	$	$	$
20% increase in annual uptake	$	$	$	$	$	$
bezlotoxumab given at each CDI episode (base case one dose per lifetime)[a]	$	$	$	$	$	$

[a] Estimated by adding the estimated number of patients treated with bezlotoxumab who experienced CDI recurrence to the total number of patients being treated each year

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

6.47 The resubmission's financial estimates were most sensitive to the assumptions used to derive the eligible population including uptake rates, CDI recurrence rate and ratio of vancomycin to metronidazole use. The cost estimates were likely underestimated because:

- Based on the current requested restriction, repeated doses of bezlotoxumab will be permitted 90 days after the index CDI episode, which was not accounted for in the financial estimates. Instead, the estimates were based on the assumption of one treatment per lifetime per patient.
- The total number of CDI episodes was estimated based on vancomycin prescriptions supplied (plus an additional 42.6% to account for episodes treated with metronidazole, given the assumed 57.4:42.6 split of vancomycin to metronidazole). As noted by DUSC, vancomycin use in Australia is restricted to pseudomembranous colitis, which only accounts for approximately 10% of CDI diarrhoeas. If, therefore, 90% of CDI cases are treated with metronidazole, the number of CDI episodes requiring antibiotic treatment may be significantly underestimated in the financial estimates (eg. assuming 90% of CDI cases will be treated with metronidazole, the eligible population for antibiotic therapy in Year 1 increased from less than 10,000 patients estimated by the submission to 10,000 – 50,000 patients, an increase of 474%). Moreover, given high risk status is to be

determined at the discretion of the treating clinician, and the drug was well tolerated in the trials, clinicians might treat (or retreat) more patients.

- Only CDI episodes treated in the outpatient setting were used to predict the eligible population. However, the requested restriction was for the total patient population at high risk of CDI recurrence. Inpatients may also be eligible to receive bezlotoxumab upon discharge from hospital.
- Recurrence rates may be lower in Australia compared to the trials; this may impact the utilisation of bezlotoxumab and hence financial estimates.
- Cost of medical services in patients treated with bezlotoxumab who experience infusion specific adverse events was not accounted for in the financial estimates but was included in the economic evaluation.
- Both DUSC and PBAC had also previously noted a number of other concerns for utilisation in the November 2017 submission (p20, Bezlotoxumab November 2017 PSD), that still apply to the current resubmission:
  - The proposed place in therapy for bezlotoxumab is for prevention of CDI, but there is a risk that bezlotoxumab might be used as a treatment where there is unknown efficacy.
  - The listing of bezlotoxumab could change clinical practice and antibiotic prescribing patterns.
  - In aged care facilities, there is a risk of antibiotic resistance and concurrent use of other biologics, with unknown implications.
  - FMT is an alternative procedure for prevention of CDI recurrence and has an observed high cure rate.
  - It is difficult to predict the impact of future outbreaks of CDI and that is an area of uncertainty in the financial estimates.

6.48 The PBAC considered that the financial implications remained highly uncertain and likely an underestimate. Further, the PBAC considered that in the context of the modest clinical benefit, the estimated financial impact presented a considerable opportunity cost.

Financial Management – Risk Sharing Arrangements

6.49 The resubmission proposed a special pricing arrangement with effective price for bezlotoxumab of $[redacted] per vial (public hospitals) (versus a published price of $[redacted]), which was [redacted]% lower than the November 2017 submission. The financial estimates in the resubmission were based on the effective prices.

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 modest clinical benefit, uncertain and unfavourable cost-effectiveness, and considerable opportunity cost.

7.2 The PBAC considered that it may be reasonable to limit use to patients at high risk of recurrence and noted that limiting use to this population resulted in a marginal increase in the difference between bezlotoxumab and SoC in the risk of CDI recurrence at 12 weeks. However, the PBAC considered that although statistically significant, a reduction in risk of 12.8 percentage points (95%CI: -17.6, -8.0) was modest. The PBAC further noted that the upper 95% confidence interval only met the minimum of the submission defined minimum clinically important difference of 8-9 percentage points. On this basis the PBAC considered that the claim of superior comparative efficacy for bezlotoxumab compared to SoC was reasonable, but that the magnitude of benefit was modest.

7.3 The PBAC noted that the submission did not present any safety data for the high risk population and considered that rates of adverse events may be higher in this population. This was particularly relevant in the context of the higher incidence of heart failure in bezlotoxumab treated patients compared to placebo treated patients in MODIFY I and II 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. The PBAC also recalled that it previously considered that because SoC does not require an infusion, patients treated with bezlotoxumab may suffer additional infusion related adverse events. The PBAC therefore considered that a claim of inferior comparative safety would be more reasonable.

7.4 The PBAC considered that the generalisability of the study population to the Australian population, and the intended PBS population was uncertain, primarily because of potential differences in the pathogenicity of circulating strains of *C. diff*. The PBAC also noted that the economic model was highly sensitive to changes in the baseline and recurrent CDI mortality rates, and that the clinical trials did not demonstrate a mortality benefit for bezlotoxumab compared to SoC. On this basis, the PBAC considered that more conservative estimates of mortality should be used. Similarly, the PBAC noted that the economic model was sensitive to the assumed risk of recurrence and considered that given the issues with generalisability of the clinical data presented, and variability in recurrence rates presented in the literature, that a more conservative approach should be taken.

7.5 The PBAC agreed with the ESC that it was inappropriate for the hospitalisation costs to be multiplied by the ratio of the length of stay, as hospital costs tend to be higher during the initial period.

7.6 The PBAC considered that the most informative analysis for decision-making was to apply the following parameters: 10 year time horizon, HR for mortality due to CDI 1.12, 2.5% mortality without CDI recurrence, lower recurrence rates for SoC (17.5%) and bezlotoxumab (9.8%), hospitalisation costs as per AR-DRG. The PBAC noted that applying these parameters in a sensitivity analysis resulted in an ICER per QALY of more than $200,000.

7.7 The PBAC considered that the estimates of utilisation and financial impact to the PBS remained uncertain, and were likely an underestimate. The PBAC also noted that the costs of repeat administration, treatment of infusion reactions, or other AEs were not included in the financial estimates. The PBAC also considered that in the context of a modest clinical benefit, this represented a high opportunity cost.

7.8 The PBAC noted that the resubmission proposed a price reduction compared to the November 2017 submission, but considered that this was insufficient to address the remaining concerns regarding the unfavourable and uncertain incremental cost-effectiveness and the high and uncertain financial impact.

7.9 The PBAC advised that any future submission would require a risk sharing arrangement with a cap to address overall utilisation as well as to manage the risk of repeat doses, and that a price reduction would be required to address the uncertainties with regard to the incremental cost-effectiveness of bezlotoxumab treatment for CDI.

7.10 The PBAC noted that this submission was eligible for 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 by the PBAC outcome for bezlotoxumab and is working with government towards making this treatment option available for patients with *Clostridium difficile* infection in Australia.