

## 5.03 BEZLOTOXUMAB, Concentrated vial for infusion 1,000mg/40mL, Zinplava<sup>®</sup>, Merck Sharp & Dohme (Australia) Pty Ltd

### 1 Purpose of Application

1.1 Section 100, Authority Required listing was requested for bezlotoxumab for prevention of *Clostridium difficile* infection (CDI) recurrence in patients receiving antibiotic therapy for CDI. Bezlotoxumab has not been considered by the PBAC previously.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with a confirmed diagnosis of CDI who are receiving oral antibiotics
Intervention	Bezlotoxumab 10 mg/kg as a single IV administration
Comparator	Placebo/SoC antibiotics only
Outcomes	Prevention of recurrence of CDI
Clinical claim	In patients with CDI, bezlotoxumab with SoC is more effective than SoC alone at preventing recurrence of CDI infection with a safety profile similar to placebo.

Abbreviation: CDI = clostridium difficile infection, IV = intravenous, SoC=standard of care

Source: Table 1.1-1, p 10 of the submission

### 2 Requested listing

Suggestions and additions proposed by the Secretariat to the revised listing proposed in the pre-sub-committee response (PSCR) are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – November 2017 PBAC Meeting

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	\$ [REDACTED] <sup>1</sup> \$ [REDACTED] <sup>2</sup>	Zinplava Merck Sharp & Dohme

Category / Program:	Section 100 Authority Required
PBS Indication:	Clostridium Difficile Infection
Treatment phase:	Initial
Restriction:	Authority required
Treatment criteria:	Patients must be receiving oral antibiotic therapy
Clinical criteria:	<p>Patients must have Clostridium Difficile Infection confirmed with PCR or EIA or pseudomembranous colitis  AND  Patient must be <del>and be</del> at a high risk of recurrence. High risk is defined by the presence of one or more of the following factors:  Older age (<math>\geq 65</math> years)  OR  History of CDI in the past 6 months  OR  Clinically severe CDI  OR  Hypervirulent strain (027, 078, or 244 ribotypes)  OR  Compromised immunity</p>
Prescriber instructions:	<p>High risk is defined by the presence of one or more of the following factors:  Older age (<math>\geq 65</math> years)  Age 65 years or older, history of CDI in the past 6 months, clinically severe CDI, hypervirulent strain (027, 078, or 244 ribotypes), or compromised immunity</p>
Administrative Advice:	The dose is limited to one per patient lifetime.

1 Public hospital; 2 Private hospital

PCR = Polymerase Chain Reaction, EIA = Enzyme Immunoassay

- 2.1 The basis for the requested listing was cost effectiveness of bezlotoxumab plus standard of care antibiotic treatment (SoC) versus SoC alone.
- 2.2 There were two main inconsistencies between the submission's proposed clinical management algorithm, the proposed TGA indication, the clinical evidence, and the requested PBS listing:
  - The requested restrictions did not require patients to have severe or recurrent CDI. Although this was consistent with the clinical evidence and the proposed TGA indication, it conflicted with the submission's claims regarding how bezlotoxumab will be used in practice and the clinical recommendations by the FDA and EMA. The PSCR proposed to alter the restriction to limit access to patients who are at 'high risk' of recurrence of CDI, specifically: older age ( $\geq 65$  years); history of CDI in the past 6 month; clinically severe CDI; hypervirulent strain (027, 078, or 244 ribotypes); or compromised immunity. The ESC agreed that restricting treatment to the high risk sub-group may be more appropriate. However, both the PBAC and ESC noted that not all of the high risk factors proposed for inclusion in the restriction showed a statistically or clinically meaningful reduction in CDI recurrence, and therefore the revised restriction may not capture the most appropriate population. The PBAC considered that the definition of what would constitute 'high risk' was unclear and that there was a risk of use outside this population to lower risk groups. The PBAC considered that although some ribotypes were known risk factors for recurrence, it

is unlikely that the ribotype would be known at the time of treatment. The PBAC also considered that the clinical criteria should require patients to have a confirmed case of toxin B positive CDI.

- While the submission claimed bezlotoxumab is not expected to be used more than once in a patient's lifetime, the wording in the requested listing did not prohibit use of bezlotoxumab for subsequent infections. The PSCR proposed new wording in the restriction to limit it to single lifetime use. However, given bezlotoxumab was well tolerated in the clinical trials with low rates of adverse events, repeat dosing is considered likely, and the proposed wording may not be sufficient to address this issue. The first round ACM clinical evaluation also considered patients may be given repeat dosing if they develop CDI recurrence or new CDI; the draft product information (PI) was silent on the issue of re-dosing. The PBAC considered it likely that dosing more than once per lifetime for a further recurrence or a new CDI would occur.
- 2.3 The dose of bezlotoxumab is 10 mg/kg as a single dose intravenous infusion via a central line or peripheral catheter over 60 minutes. It is administered concurrently with antibiotics for treatment of CDI. The optimal timing of bezlotoxumab in relation to antibiotics however was unclear (i.e., at the start, middle or end of course) and is not stated in the draft PI. In the trials the majority of patients received bezlotoxumab between days 3-6 after commencing antibiotic therapy.

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

### 3 Background

- 3.1 The submission was lodged under the TGA/PBAC parallel process. The submission indicated (p20) that TGA approval is expected in mid-November 2017. At the time of PBAC consideration, the TGA Delegate's Overview and the Advisory Committee on Medicine (ACM) Outcome were available.
- 3.2 The indication proposed in the TGA application is: "Bezlotoxumab is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. It can be prescribed in conjunction with any standard of care antibiotic that is used for treatment of *C. difficile* infection such as metronidazole, vancomycin, or fidaxomicin." The TGA's delegate requested the ACM provide advice on whether the indication should restrict use to 'at risk patients'. The ACM agreed that the indication should restrict use in 'high risk patients' and noted that the sponsor also agreed with this modification.

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

### 4 Population and disease

- 4.1 *Clostridium difficile* (*C. difficile*) is a bacterium not normally present in the gut flora. In order for CDI to occur, the patient must first experience a disruption in the normal gut flora (e.g. from taking broad spectrum antibiotics) and then acquire *C. difficile* from an exogenous source usually via faecal-oral route (e.g. from another infected patient). Only toxin producing strains of *C. difficile* will produce disease. Symptoms

include watery diarrhoea, fever, nausea and abdominal pain. A more severe form of the infection, pseudomembranous colitis, is also found in around 10% of all *C. difficile* related diarrhoeas; this occurs when inflammatory reaction of the cells in the intestines forms a “pseudomembrane”.

- 4.2 Recurrence of CDI occurs due to persistent or newly-acquired *C. difficile* spores, whose outgrowth (leading to new toxin expression) is facilitated by gut flora disturbance caused by antibiotics. The risk of recurrence is higher in patients who are greater than 65 years of age, who are immunocompromised or have severe initial CDI.
- 4.3 CDI is more likely to occur in hospitals than in the community setting (3.65 versus 1.08 per 10,000 patient days respectively based on Slimings et al (2014)). All-cause mortality in patients hospitalised with CDI at 30 days is estimated to be between 9% and 38% (Mitchel 2012)<sup>1</sup>. Limited Australian data suggest the 30-day mortality for CDI patients in Australia may be even lower with reported rates at 2.5%<sup>2</sup> and 3.6%<sup>3</sup>.
- 4.4 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 *C. difficile* spores. Bezlotoxumab is effective against toxins from a broad range of clinical isolates of *C. difficile*. However, bezlotoxumab does not enhance the efficacy of antibiotics used to treat CDI and only prevents recurrence of CDI after antibiotic treatment is complete.
- 4.5 There is no expected change to the diagnostic algorithms or choice of antibiotic therapy for CDI with the use of bezlotoxumab. However, it is a potential option to prevent future recurrence. The PBAC noted that ribotyping is not part of the diagnostic algorithm for CDI so including infection with virulent ribotypes as criterion for treatment could result in a change in practice and incur a cost to the health system.
- 4.6 The submission presented separate algorithms for severe and non-severe CDIs. The main difference between the submission’s current and proposed algorithms was that if bezlotoxumab is PBS listed, it will be administered for all severe CDI (i.e. initial and recurrent episodes) and only for recurrent mild/moderate CDI. The submission’s algorithm also indicated that bezlotoxumab would mostly be administered alongside oral vancomycin, which is indicated for recurrent or severe initial CDI. This was considered unlikely given the trial evidence suggested bezlotoxumab to be effective in patients both with and without prior CDI episodes and in those with severe and mild/moderate CDI. In fact, a similar proportion of patients in the trials had received

---

<sup>1</sup> Mitchell BG, Gardner A. Mortality and *Clostridium difficile* infection: a review. Antimicrobial Resistance and Infection Control 2012 1:20. Available from [Antimicrobial Resistance and Infection Control website](#) accessed 3/8/17

<sup>2</sup> Foster NF, Collins DA, Ditchburn SL, Duncan CN, van Schalkwyk JW, Golledge CL, Keed AB, Riley TV. Epidemiology of *Clostridium difficile* infection in two tertiary-care hospitals in Perth, Western Australia: a cross-sectional study. New Microbes New Infect. 2014 May;2(3):64-71. doi: 10.1002/nmi2.43. Epub 2014 Apr 1.

<sup>3</sup> Department of Health, Surveillance snapshot of *Clostridium difficile* infection in hospitals across Queensland detects binary toxin producing ribotype UK 244, 24 December 2014. Available from [Department of Health website](#) accessed 16/8/17

oral metronidazole compared to oral vancomycin (both approximately 50%). The PBAC did not consider it would be appropriate to limit use of bezlotoxumab based on the antibiotic therapy the patient was using to treat the current CDI.

## 5 Comparator

- 5.1 Placebo (or SoC antibiotics). The PBAC considered that the nominated comparator was appropriate. The submission also acknowledged that faecal microbiota transplant (FMT) is an alternative procedure used for prevention for recurrent CDI. However as FMT is yet to be trialled in large randomised trials and is a “last resort” option, the submission argued that it would not be the most relevant comparator for bezlotoxumab. It is not clear from the submission whether FMT and bezlotoxumab are likely to be used concurrently in clinical practice or whether FMT would be used if bezlotoxumab failed to prevent recurrence.
- 5.2 A growing body of evidence also suggests that some strains of probiotics may be effective in primary prevention of *C. difficile* associated diarrhoeas (CDAD). A meta-analysis by Lau and Chamberlain (2016), including evidence from 26 RCTs enrolling a total of 7,597 patients, concluded that probiotic use reduced the risk of developing CDAD by 60.5% (relative risk [RR] =0.395; 95% confidence interval [CI], 0.294–0.531; P<0.001). Probiotics were found to be beneficial in both adults and children (59.5% and 65.9% reduction, respectively), especially among hospitalised patients. However one recent review suggested probiotics were no different to placebo in primary prevention among hospitalised patients >65 years<sup>4</sup>, so evidence in this area is still emerging. Although not a direct comparator, the effect of probiotics at reducing primary infections of CDI is likely to also impact on the efficacy of bezlotoxumab for secondary prevention.

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

## 6 Consideration of the evidence

### Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and how the drug would be used in practice, and addressed other matters in response to the Committee’s questions.

The PBAC considered that the hearing was informative as it allowed the clinician to provide evidence that CDI had a considerable impact on quality of life, which was a relevant consideration. The committee also noted the clinician’s advice that mortality rates varied between countries, that there appears to be worse mortality with the highly virulent ribotypes, and that Australia did not have a high incidence of the most virulent ribotype. The PBAC therefore felt that estimates of case fatality from overseas are not directly transferrable to the Australian population.

---

<sup>4</sup> Vernaya M, McAdam J, Hampton MD. Effectiveness of probiotics in reducing the incidence of Clostridium difficile-associated diarrhea in elderly patients: a systematic review. JBI Database System Rev Implement Rep 2017;15:140-164.

## Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual (1) via the Consumer Comments facility on the PBS website, which described a range of benefits of treatment with bezlotoxumab, including the ability to return to normal life and avoidance of further CDI.

## Clinical trials

- 6.3 The submission was based on two direct randomised trials (MODIFY I and MODIFY II) which compared bezlotoxumab + SoC to placebo + SoC (N=807 and 806 in MODIFY I and MODIFY II respectively). MODIFY I also included two additional arms which administered actoxumab + SoC (N=242) and actoxumab + bezlotoxumab + SoC (N=403) whilst MODIFY I included one additional treatment arm which administered actoxumab + bezlotoxumab + SoC (N=397). Actoxumab was found to be ineffective in preventing of CDI recurrence in the trials when given alone and provided no additional benefit when given with bezlotoxumab, it is also not the subject of or a comparator for this submission. Its results are therefore irrelevant to the current submission and are not presented.
- 6.4 MODIFY I and MODIFY II were similarly designed, randomised, double blind and placebo controlled trials. In the relevant treatment arms, adult patients with CDI received a single dose of bezlotoxumab 10 mg/kg or placebo (normal saline) infused over 60 minutes, alongside oral SoC antibiotics (metronidazole, vancomycin or fidaxomicin chosen by their treating physician for 10-14 days). Patients who were receiving oral vancomycin or fidaxomicin could also receive IV metronidazole.
- 6.5 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
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-3067 (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).  Wilcox et al., Bezlotoxumab for Prevention of Recurrent <i>Clostridium difficile</i> Infection.	09/10/2015  New England Journal of Medicine 2017; 376:4 (305-317)
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)  Wilcox et al., Bezlotoxumab for Prevention of Recurrent <i>Clostridium difficile</i> Infection.	02/11/2015  New England Journal of Medicine 2017; 376:4 (305-317)

Source: Table 2.2-1, p30 of the submission, secondary publications were removed from the Table.

- 6.6 The key features of the direct randomised trials are summarised in the table below.

**Table 3: Key features of the included evidence bezlotoxumab vs. placebo (ITT population)**

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes <sup>3</sup>	Use in modelled evaluation
MODIFY I	1452 <sup>1</sup> 807 <sup>2</sup>	R, DB 12 weeks	Low	CDI (without regard to severity) being treated with either oral metronidazole, vancomycin or fidaxomicin	CDI recurrence Global cure	CDI recurrence
MODIFY II	1203 <sup>1</sup> 806 <sup>2</sup>					

<sup>1</sup> Includes patients in all arms.

<sup>2</sup> Only patients who were treated with placebo or bezlotoxumab alone

<sup>3</sup> Outcomes were for the Full Analysis Set (FAS) population, which included treated patients with confirmed CDI and had started SoC antibiotics before or within 1 day after receiving the trial treatment.

DB=double blind; R=randomised.

Source: compiled during the evaluation

6.7 The submission argued that CDI recurrence is the most relevant outcome from the trials as i) bezlotoxumab does not impact on the baseline episode of CDI, and ii) CDI recurrence was the primary outcome, so the trials were powered to detect a difference in this outcome. As there is no commonly accepted minimum clinically important difference (MCID) for CDI recurrence, based on assumptions used in the sample size calculation of the MODIFY trials, the submission nominated a MCID of an 8-9% reduction in the percentage of patients with CDI recurrence between bezlotoxumab and placebo. The submission did not provide any further discussion on this MCID; however, given that the longevity of the effect is unknown beyond one year, it is uncertain whether an 8-9% reduction would be clinically significant. The PBAC agreed with the ESC that an improvement of 8-9% was modest, and it was uncertain whether this was clinically meaningful.

6.8 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).

### Comparative effectiveness

6.9 The submission presented data based on the full analysis set (FAS), which included patients who received treatment with bezlotoxumab + SoC or placebo + SoC, with a positive *C. difficile* stool test and received SoC antibiotics before or within 1 day after receiving the trial treatment. Although an intention to treat analysis would be preferred, since only a small proportion of randomised patients were excluded from the FAS (3.6%) and the proportions were even between the bezlotoxumab and placebo groups, this was unlikely to significantly bias the results.

6.10 The primary outcome in MODIFY I and MODIFY II was CDI recurrence at 12 weeks. CDI recurrence was defined as developing a new episode of CDI, after clinical cure was achieved (clinical cure was defined as no diarrhoea for 2 consecutive days after completion of SoC antibiotic therapy administered for ≤16 days). A secondary outcome, global cure, was defined as clinical cure plus no CDI recurrence. The results of MODIFY I and MODIFY II are presented in Table 4.

Table 4: CDI Recurrence and Global cure rates at 12 weeks in MODIFY I and MODIFY II FAS

	Bezlotoxumab n/N (%)	Placebo n/N (%)	Adjusted % Risk Difference <sup>^</sup> (95% CI)	Relative risk* (95% CI)
<b>1: CDI Recurrence at 12 weeks</b>				
MODIFY I	67/386 (17.4)	109/395 (27.6)	<b>-10.1% (-15.9, -4.3)</b>	<b>0.63<sup>s</sup> (0.48, 0.82)<sup>s</sup></b>
MODIFY II	62/395 (15.7)	97/378 (25.7)	<b>-9.9% (-15.5, -4.3)</b>	<b>0.61<sup>s</sup> (0.46, 0.81)<sup>s</sup></b>
Total#	129/781 (16.5)	206/773 (26.6)	<b>-10.0% (-14.0, -6.0)</b>	<b>0.62<sup>s</sup> (0.51, 0.75)<sup>s</sup></b>
<b>Subgroup results: CDI Recurrence amongst patients who attained clinical cure of initial episode at 12 weeks</b>				
MODIFY I	67/299 (22.4)	109/327 (33.3)	<b>-10.8% (-17.7, -3.8)</b>	<b>0.67<sup>s</sup> (0.52, 0.87)<sup>s</sup></b>
MODIFY II	62/326 (19.0)	97/294 (33.0)	<b>-13.7% (-20.4, -6.9)</b>	<b>0.58<sup>s</sup> (0.44, 0.76)<sup>s</sup></b>
Total#	129/625 (20.6)	206/621 (33.2)	<b>-12.2% (-17.1, -7.4)</b>	<b>0.62<sup>s</sup> (0.51, 0.75)<sup>s</sup></b>
<b>2: Clinical cure of initial episode at 12 weeks</b>				
MODIFY I	299/386 (77.5)	327/395 (82.8)	-5.3% (10.9, 0.3)	0.94 <sup>s</sup> (0.87, 1.00) <sup>s</sup>
MODIFY II	326/395 (82.5)	294/378 (77.8)	4.8% (-0.9, 10.4)	1.06 <sup>s</sup> (0.99, 1.14) <sup>s</sup>
Total#	625/781 (80.0)	621/773 (80.3)	-0.3% (-4.3, 3.7)	1.00 <sup>s</sup> (0.95, 1.05) <sup>s</sup>
<b>3: Global cure at 12 weeks (Clinical cure of initial episode and no CDI recurrence)</b>				
MODIFY I	232/386 (60.1)	218/395 (55.2)	4.9% (-2.1, 11.7)	1.09 <sup>s</sup> (0.97, 1.23) <sup>s</sup>
MODIFY II	264/395 (66.8)	197/378 (52.1)	<b>14.6% (7.7, 21.4)</b>	<b>1.28<sup>s</sup> (1.14, 1.45)<sup>s</sup></b>
Total#	496/781 (63.5)	415/773 (53.7)	<b>9.7 (4.8, 14.5)</b>	<b>1.18<sup>s</sup> (1.09, 1.29)<sup>s</sup></b>

# pooled results of MODIFY I and MODIFY II

<sup>^</sup> adjusted for stratification factors of hospitalisation status and standard of care therapy.

\* <sup>s</sup> values calculated during evaluation using StatsDirect v2.7.8 (adjustment for stratification not able to be applied). Text in bold indicate statistically significant results.

Source: Table 11-1, p206 MODIFY I CSR, and table 11-1, 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).

- 6.11 Overall, CDI recurrence at 12 weeks was statistically significantly lower in patients treated with a single dose bezlotoxumab than placebo in the MODIFY trials. The pooled point estimate of the risk difference (RD) of -10.1% (95%CI: -14%, -6%) exceeded the submission's nominated MCID of 8-9%. However, the upper 95% CI (-6.0%) did not meet this threshold.
- 6.12 The magnitude of the difference between the treatment arms in terms of global cure (RD: 9.7% 95%CI: 4.8, 14.8) was smaller than the estimated difference in the primary outcome of CDI recurrence (-10.1%), and the lower 95%CI (4.8%) was also below the nominated MCID. Global cure was statistically significantly higher in bezlotoxumab treated patients in the pooled analysis and in the MODIFY II trial versus placebo. The result for MODIFY I, though numerically higher than placebo did not reach statistical significance. The submission argued this was due to a lower than expected proportion of patients achieving clinical cure in the bezlotoxumab arm of the trial. However, as evident in Table 5, there was no significant difference in the proportion of patients achieving clinical cure between bezlotoxumab and placebo in any of the trials. While these results do not support the submission's claim above, the proportion of patients achieving a clinical cure in the trial arms affirmed the claim that bezlotoxumab is not expected to change the course of disease (or rate of recovery) for the current episode of CDI infection.
- 6.13 A number of predefined subgroup analyses were presented in the submission for the outcome of CDI recurrence for the combined MODIFY I and MODIFY II population. These are summarised in Table 5.

**Table 5: CDI recurrence in subpopulations: RISK Factors for CDI Recurrence (MODIFY I and II integrated)**

Population	Bezlotoxumab n/N (%)	Placebo n/N (%)	Risk difference (95% CI) <sup>1</sup>	Relative Risk (95% CI)
All participants	129/781 (16.5)	206/773 (26.6)	<b>-10.1%<sup>§</sup> (-14.2, -6.1)<sup>§</sup></b>	<b>0.62<sup>§</sup> (0.51, 0.75)<sup>§</sup></b>
<b>Risk factors for recurrence</b>				
Older than 65 years	60/390 (15.4)	127/405 (31.4)	<b>-16.0%<sup>§</sup> (-21.7, -10.2)<sup>§</sup></b>	<b>0.4<sup>§</sup> (0.37, 0.64)<sup>§</sup></b>
No CDI in past 6 months	75/556 (13.5)	114/545 (20.9)	<b>-7.4%<sup>§</sup> (-11.9, -3.0)<sup>§</sup></b>	<b>0.64<sup>§</sup> (0.49, 0.84)<sup>§</sup></b>
≥1 CDI episode in past 6 months	54/216 (25.0)	90/219 (41.1)	<b>-16.1%<sup>§</sup> (-24.7, -7.3)<sup>§</sup></b>	<b>0.61<sup>§</sup> (0.46, 0.80)<sup>§</sup></b>
≥2 previous CDI episodes ever	29/100 (29.0)	53/126 (42.1)	<b>-13.1%<sup>§</sup> (-25.1, -0.4)<sup>§</sup></b>	<b>0.69<sup>§</sup> (0.47, 0.99)<sup>§</sup></b>
Immunocompromised	26/178 (14.6)	42/153 (27.5)	<b>-12.8%<sup>§</sup> (-21.7, -4.1)<sup>§</sup></b>	<b>0.53<sup>§</sup> (0.34, 0.82)<sup>§</sup></b>
Severe CDI; Zar score >=2	13/122 (10.7)	28/125 (22.4)	<b>-11.7%<sup>§</sup> (-21.1, -2.5)<sup>§</sup></b>	<b>0.48<sup>§</sup> (0.26, 0.86)<sup>§</sup></b>
027, 078 or 244 strain	22/102 (21.6)	37/115 (32.2)	-10.6% <sup>§</sup> (-22.1, 1.3) <sup>§</sup>	0.67 <sup>§</sup> (0.42, 1.05) <sup>§</sup>
027 strain	21/89 (23.6)	34/100 (34.0)	-10.4% <sup>§</sup> (-23.0, 2.6) <sup>§</sup>	0.69 <sup>§</sup> (0.44, 1.09) <sup>§</sup>
<b>Stratification variables</b>				
Inpatient	73/530 (13.8)	120/520 (23.1)	<b>-9.3%<sup>§</sup> (-14.0, -4.6)<sup>§</sup></b>	<b>0.60<sup>§</sup> (0.46, 0.78)<sup>§</sup></b>
Outpatient	56/251 (22.3)	86/253 (34.0)	<b>-11.7%<sup>§</sup> (-19.4, -3.8)<sup>§</sup></b>	<b>0.66<sup>§</sup> (0.49, 0.87)<sup>§</sup></b>
Metronidazole	56/379 (14.8)	85/374 (22.7)	<b>-8.0%<sup>§</sup> (-13.5, -2.4)<sup>§</sup></b>	<b>0.65<sup>§</sup> (0.48, 0.88)<sup>§</sup></b>
Vancomycin	67/372 (18.0)	114/373 (30.6)	<b>-12.6%<sup>§</sup> (-18.6, -6.4)<sup>§</sup></b>	<b>0.59<sup>§</sup> (0.45, 0.77)<sup>§</sup></b>
Fidaxomicin	6/30 (20.0)	7/26 (26.9)	-6.9% <sup>§</sup> (-29.7, 15.5) <sup>§</sup>	0.74 <sup>§</sup> (0.29, 1.88) <sup>§</sup>
<b>Geographic region</b>				
North America	69/354 (19.5)	106/366 (29.0)	<b>-9.5%<sup>§</sup> (-15.7, -3.2)<sup>§</sup></b>	<b>0.67<sup>§</sup> (0.52, 0.88)<sup>§</sup></b>
Europe	47/313 (15.0)	71/293 (24.2)	<b>-9.2%<sup>§</sup> (-15.6, -2.9)<sup>§</sup></b>	<b>0.62<sup>§</sup> (0.44, 0.86)<sup>§</sup></b>
Asia Pacific	11/79 (13.9)	21/77 (27.3)	<b>-13.3%<sup>§</sup> (-26.1, -0.6)<sup>§</sup></b>	<b>0.51<sup>§</sup> (0.27, 0.97)<sup>§</sup></b>
Latin America	2/30 (6.7)	8/35 (22.9)	-16.2% <sup>§</sup> (-33.8, 1.8) <sup>§</sup>	0.29 <sup>§</sup> (0.07, 1.10) <sup>§</sup>

<sup>1</sup> Based on the Miettinen and Nurminen method without stratification.

Text in bold indicate statistical significance. § indicates values calculated during evaluation using StatsDirect

Source: Figure A, Wilcox et al 2017

6.14 The PSCR provided a new analysis of the rate of recurrence based on their revised listing population of ‘high risk’ patients to support their revised restriction. The results indicated a slightly larger reduction in recurrence in all high-risk patients (█% [95% CI: █]; Table 6) with the lower limit now closer to the proposed MCID. These results could not be verified. Furthermore, as shown in the sub-group analysis in Table 5 above, some of the high risk groups nominated for inclusion in the restriction had upper 95% CIs that crossed over the pre-specified MCID (CDI episode in past 6 months, immunocompromised, and severe CDI patients), or were not statistically significant (hypervirulent CDI strain). The PBAC considered that there was little evidence that the variation in absolute risk difference observed across patient subgroups was beyond that expected by chance.

**Table 6: Recurrence rates for all high risk & high risk outpatients**

	Bezlotoxumab n/N (%)	Placebo n/N (%)	Risk Difference (95% CI) <sup>§</sup>
High Risk Patients‡	█	█	█
Outpatient AND High Risk‡	█	█	█

§ Based on the Miettinen and Nurminen method without stratification.

‡ Predefined risk factors include CDI history in the past 6 months, severe CDI at baseline (per Zar score), Age ≥ 65 years, have a hypervirulent strain (027, 078, or 244 ribotypes) at baseline, and/or immunocompromised.

6.15 The published report stated that 77% of the MODIFY trial populations had one or more risk factors for recurrent CDI or for adverse outcomes related to CDI (Wilcox 2015). Across these pre-specified risk subpopulations, recurrent CDI infections were consistently lower in the bezlotoxumab treatment arm than placebo; the differences also remained statistically significant for all subgroups except for patients with infection caused by *C. difficile* strain 027 and patients with infection caused by strain 027, 078, or 244. However, the numbers of patients in these bacterial strain

subgroups were small. In comparison to the overall trial result, the differences in CDI recurrence between bezlotoxumab and placebo treated patients were consistently higher in those with risk factors, particularly those aged >65 years (RD (95%CI): -16.0% (-21.7, -10.2)) and have had >1 CDI episode in the last 6 months (RD (95%CI): -16.1% (-24.7,-7.3)). In contrast, the effect size for bezlotoxumab versus placebo was lower in patients with no CDI in the past 6 months RD (95%CI): -7.4% (-11.9,-3.0).

- 6.16 There is limited Australian data to permit a direct comparison of CDI recurrence risk with the trial population, however two studies sourced during the evaluation suggested that the risk of recurrence in the Australian population in some aspects may be lower than in the MODIFY trials. The study reported that across 175 hospitals in a 2 months period in Queensland in early 2012<sup>5</sup>, only 11.9% (20/168) of all patients who experienced a CDI episode have had a prior episode of CDI in the past 2 months, whereas 22.8% (375/1554) of patients in the combined MODIFY trials reported CDI in the past 3 months. One Western Australian hospital cross section study (Foster 2014) also reported that only 17.5% (14/80) of CDI patients in the study reported any prior history of CDI. However, it was not possible to conduct a comparison of the high-risk groups from the trial to a similar high-risk group in the Australian population.
- 6.17 The submission claimed that patients identified as ‘outpatients’ in MODIFY I and MODIFY II would be most relevant to the requested PBS listing since they represent patients who will be treated with bezlotoxumab in an outpatient setting. This was not an appropriate assumption, in the trials this classification was based on a patient’s hospitalisation status at randomisation, and not where the patient was treated. In addition, some ‘outpatients’ had received treatment in the hospital and vice versa. Overall, it was considered unlikely that the ‘outpatients’ subgroup in the trials would be representative of the PBS population. A brief comparison of baseline demographics by hospitalisation subgroup is presented below. As the clinical study report and published report do not report patient demographics by hospitalisation subgroup, these numbers were not able to be independently verified during the evaluation.

**Table 7: Comparison of patient demographics by hospitalisation status**

Parameter	Outpatient	Inpatient	Whole trial population
<b>Patient demographics</b>			
Age of population (years)	56.7	65.6	62.7
Proportion of Female patients	63.3%	54.5%	57.3%
Proportion with mild/moderate CDI in index case	96.4%	77.2%	83.4%
Proportion of recurrence CDI which is severe	1.6%	16.2%	9.9%

Source: extracted from Section 3 Model spreadsheet

- 6.18 Patients classified as ‘outpatients’ in the trials were younger with a greater proportion of patients with mild/moderate disease and a lower proportion of patients with recurrent CDI which is severe. Despite this, CDI recurrence was greater in patients classified as ‘outpatient’ in the trials compared to ‘inpatients’. The risk

<sup>5</sup> Department of Health, Surveillance snapshot of Clostridium difficile infection in hospitals across Queensland detects binary toxin producing ribotype UK 244, 24 December 2014. Available from [Department of Health website](#) accessed 16/8/17

difference in CDI recurrence between bezlotoxumab and placebo was also greater in the 'outpatient' subgroup -11.7% (95%CI: -19.4,-3.8) versus -9.3% (95%CI: -14.0,-4.6) in the 'inpatient' group and -10.1 (95%CI: -14.2, 6.1) in the whole trial population. The PSCR (p2) also presented a sub-group analysis of the 'high-risk outpatient' population in the trial (Table 6), which showed a slightly greater reduction in the risk of recurrence compared to the total high-risk trial population. However, PBAC agreed with the ESC that for the reasons outlined above the outpatient sub-population was inappropriate, and therefore the whole of trial high-risk group should be used. The PBAC noted that the reduction in risk of recurrence was slightly greater in the high-risk subgroup of patients, but that the difference remained modest.

- 6.19 The submission also presented data from an extension study of MODIFY II, in which some patients (100 patients treated with bezlotoxumab and 83 patients treated with placebo) were observed for an additional nine months after MODIFY II for a total of 12 months, however the inclusion criteria for the MODIFY II extension study were unclear. In all patients observed in the MODIFY II extension study, only one additional case of CDI recurrence (in a patient treated with placebo) was reported after Week 12. Based on this evidence, the submission assumed that CDI recurrence was unlikely to occur after 12 weeks of the index CDI episode and that bezlotoxumab prevents rather than just delay CDI recurrence beyond 12 weeks. While this was reasonable, it was unknown whether this effect will persist beyond one year and up to 10 years (as was estimated in the base case of the economic evaluation).

### Comparative harms

- 6.20 Overall, there were no statistically significant differences in adverse events (AEs) between bezlotoxumab and placebo treatment groups in MODIFY I and MODIFY II. The most commonly reported adverse events in the MODIFY I and MODIFY II trials for bezlotoxumab and placebo were infusion specific AEs (9%), nausea (2%), headache (2%), dizziness (1%), fatigue (1%) and pyrexia (1%). The most frequently reported AEs with a fatal outcome in the bezlotoxumab and placebo treatment arms of the trials were septic shock (0.8%), sepsis (0.8%), pneumonia (0.6%), cardiac failure (0.4%), and respiratory failure (0.4%).
- 6.21 With respect to infusion specific AEs (including local infusion site as well as systemic AEs), although not statistically significant, there was a trend for more events in patients treated with bezlotoxumab compared to placebo (10% vs. 8%;  $p=0.056$ ). Furthermore, it should be noted that in clinical practice, SoC would not require all patients to have an infusion and, as such, most of the infusion specific AEs from the administration of bezlotoxumab could be considered additional to current SoC. The PBAC agreed with the ESC that it was more reasonable to assume that the rate of infusion reactions for bezlotoxumab would be closer to 10% and be additional to SoC.
- 6.22 There were no statistically significant differences in the number of deaths reported between treatment groups in MODIFY I and MODIFY II. The numbers of deaths were low in the MODIFY trials and were numerically similar between placebo and bezlotoxumab at Week 12 (pooled MODIFY I and MODIFY II, 59/781 (7.6%) and 56/786 (7.1%), respectively).

6.23 In the US prescribing information, FDA noted that heart failure was reported more commonly in patients with a history of congestive heart failure (CHF) taking bezlotoxumab, and bezlotoxumab should only be used if benefits outweigh the risk.

## Benefits and harms

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

**Table 8: Summary of comparative benefits and harms for bezlotoxumab and SoC**

<b>Benefits</b>						
<b>CDI recurrence at 12 weeks</b>						
Trial	Bez + SoC	SoC	RR (95% CI)	Events/100 patients <sup>1</sup>		RD (95% CI)
				Bez + SoC	SoC	
MODIFY I	67/386	109/395	0.63 (0.48,0.82)	17.4	27.6	-10.1(-15.9,-4.3)
MODIFY II	62/395	97/378	0.61 (0.46,0.81)	15.7	25.7	-9.9(-15.5,-4.3)
Pooled	129/781	206/773	0.62 (0.51,0.75)	16.5	26.6	-10.0(-14.0,-6.0)
<b>Global cure at 12 weeks</b>						
MODIFY I	232/386	218/395	1.09 (0.97,1.23)	60.1	55.2	4.9 (-2.1,11.7)
MODIFY II	264/395	197/378	1.28 (1.14,1.45)	66.8	52.1	14.6 (7.7,21.4)
Pooled	496/781	415/773	1.18 (1.09,1.29)	63.5	53.7	9.7 (4.8,14.5)
<b>Harms</b>						
	Bez + SoC	SoC	RR (95% CI)	Events/100 patients <sup>1</sup>		RD (95% CI)
				Bez+SoC	SoC	
<b>Infusion specific adverse events (e.g. nausea, dizziness, headache, fatigue and pyrexia)</b>						
MODIFY I and II (pooled)	81/786 (10)	0/781 <sup>2</sup>	162.0 <sup>§</sup> (21,NA) <sup>§</sup>	10.3	0	10 <sup>§</sup> (8.3,12.6) <sup>§</sup>

<sup>1</sup>At 12 weeks of follow-up for all trials

<sup>2</sup>Comparator in practice is no treatment therefore do not expect any infusion related adverse events

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

<sup>§</sup> indicates values calculated during evaluation

Source: Compiled during the evaluation using data from Table 11-1, p206 MODIFY I CSR, and table 11-1, 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 Table 2.5-13, p61 of the submission

6.25 On the basis of direct evidence presented by the submission, for every 100 patients treated with bezlotoxumab plus SoC in comparison to SoC, after 12 weeks:

- Approximately 10 fewer patients would have CDI recurrence;
- Approximately 10 more patients would have achieved global cure (clinical cure of initial CDI episode plus no CDI recurrence); and
- Approximately 10 more patients would experience an infusion specific adverse event.

6.26 The PBAC noted that based on the sub-group of high-risk patients, for every 100 'high risk' patients treated with bezlotoxumab plus SoC compared to SoC after 12 weeks, approximately 13 fewer patients would have CDI recurrence. No analysis was provided with respect to rates of global cure or infusion reactions in this subgroup.

## Interpretation of clinical evidence

6.27 The submission claimed that treatment with bezlotoxumab plus SoC antibiotics compared to SoC antibiotics alone is superior in preventing CDI recurrence at 12 weeks and non-inferior in terms of safety.

6.28 In terms of efficacy, bezlotoxumab was superior to placebo in preventing CDI recurrence in the trials, with an absolute difference in recurrence of -10.1%

(95%CI: -14.2, -6.1). However, it is uncertain whether this difference is clinically meaningful as the lower 95%CI did not meet the submission nominated MCID of 8-9% reduction versus placebo.

- 6.29 With respect to the ‘high-risk’ subgroup of patients nominated in the PSCR, the data indicates bezlotoxumab was superior to placebo in preventing CDI recurrence in the trials, with an absolute difference in recurrence of █% (95%CI █). These results have not been verified, and it is unclear whether this difference is clinically meaningful.
- 6.30 In terms of safety, the conclusion was supported when compared to the administered placebo infusion in the MODIFY I and MODIFY II trials, but it may not be supported when compared to current SoC antibiotics alone, where patients may not receive any infusions. Compared to patients who do not receive any infusions in current SoC, patients treated with bezlotoxumab may suffer additional infusion related adverse events so bezlotoxumab may not actually be non-inferior in safety. Moreover, there may be specific concerns for patients with a history of CHF, which was not discussed by the submission.
- 6.31 The PBAC considered that while the claim of superior comparative effectiveness was supported by the data based on the pre-defined superiority margin, the clinical relevance of this difference was unclear.
- 6.32 The PBAC considered that the claim of non-inferior comparative safety was not supported by the data when compared to oral antibiotics alone (i.e. no placebo infusion).

### **Economic analysis**

- 6.33 A stepped cost utility analysis was presented, based on results from the MODIFY I and MODIFY II trials. Key components of the economic evaluation are summarised in Table 9. The PSCR presented a new economic analysis based on restricting the PBS indication to the high-risk patients only. This new analysis retained the same structure of the model, but changed inputs regarding patient age, gender split, proportion entering with mild/moderate or severe CDI, proportion of subsequent recurrences that were severe, rate of recurrence for those who received bezlotoxumab, and rate of recurrence in those who received no treatment. While the revised ICER based on these new inputs could be confirmed, the choice of inputs could not.

**Table 9: Summary of model structure and rationale**

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Cost per CDI recurrence avoided; cost per life year (LYG) gained; cost per quality adjusted life year (QALY) gained.
Time horizon	A 10 year time horizon was presented as the base case. A 5 year time horizon and a lifetime horizon were tested in sensitivity analysis. Given there is no clinical trial data on CDI recurrence beyond 1 year and the main trial outcomes were measured at 12 weeks a 10 year time horizon may not be appropriate. The model was very sensitive to the assumed time horizon, halving the time horizon to 5 years doubled the ICER to over \$100,000 per QALY gained.
Methods used to generate results	Markov cohort analysis.
Health states	8 main health states: 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.
Utilities	The utilities for the health states of mild/moderate CDI (0.880), severe CDI (0.817) and colectomy (0.817) were extracted from an economic evaluation reported by Bartsch 2013. The utilities for the health states clinical cure (1.0), clinical failure (0.88), post clinical failure (1.0), post colectomy (1.0) and death (0) were assumptions. Patient specific health state utilities were then estimated by multiplying these health state utilities by the age/gender population level utility values from a large international study using EQ-5D values (Szende2014). The reported CDI health state utilities were not specific to CDI and were reported for conditions associated with non-infectious diarrhoea. However, the model is not very sensitive to utility assumptions alone.
Cycle length	15 days in the first year, annual cycle length thereafter. With half cycle corrections to costs and benefits. This was reasonable given the chosen model structure.
Transition probability	Transitional probabilities were calculated from MODIFY I and MODIFY II.  The results for global cure were not applied in the model. Instead, clinical cure and CDI recurrence from the MODIFY trials were applied separately.  Efficacy estimates regarding the probability of CDI recurrence were adjusted to the 15 day cycle length in the first year of the model. The submission claimed the literature suggested most CDI recurrences occur within 30 days of the index episode and that in MODIFY I and MODIFY II 71% of all CDI recurrences across all treatment groups had occurred within the first 4 weeks following the infusion of trial medication. Based on this, the submission assumed that 100% of all CDI recurrences that occurred over 84 days in the trials will occur within the first 30 days of the initial episode of CDI in the economic evaluation. This approach favoured bezlotoxumab in the model since it allowed events to happen earlier and thus benefits to be accrued for longer.  Mortality rates were allowed to differ between bezlotoxumab + SoC and placebo + SoC arms in the first 180 days in the model assuming lower probability of deaths in the bezlotoxumab + SoC arm. These were not informed by the trials, which did not find any significant difference between bezlotoxumab and placebo in mortality, instead these were derived from Olsen 2015 and were converted to 15 day probabilities assuming constant incidence over this time. Post 180 days, mortality in the model was assumed to revert to Australian Bureau of statistics life table values. A number of issues were noted in relation to transition probabilities.

CDI = Clostridium difficile infection

Source: Table 3.1-1, p74 of the submission

- 6.34 The ESC noted that the modelled economic evaluation did not consider adverse events related to bezlotoxumab (such as infusion related events).
- 6.35 The submission's base case result was estimated for a subpopulation of patients classified as 'outpatients' in the trials. Given this is highly unlikely to reflect how bezlotoxumab will be used in practice; the results of the modelled economic evaluation were re-estimated during the evaluation using the submission's methodology for the whole trial population. As summarised in Table 10, use of

outpatient data in the modelled economic evaluation had favoured bezlotoxumab, as when the whole trial results were used the ICER increased by 14%.

6.36 The ESC considered that the total population, rather than the subpopulation of ‘outpatients’ was the appropriate population to use for the economic evaluation. The ESC also noted that in light of the revised restriction proposed in the PSCR, the economic model was amended to use updated characteristics to reflect this subgroup, as detailed in 6.29. As the structure of the model was unchanged from the original submission, the ESC noted that the issues relating to the key drivers are the same as for the modelled economic evaluation provided with the submission.

6.37 The key drivers of the model are summarised in Table 10.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	Time horizon assumed to be 5 years rather than the 10 year assumed in the base case	High (100% increase in ICER). Favoured bezlotoxumab.
Trial population	Using results for the whole trial population rather than the ‘outpatient’ population.	Moderate (~14%). Favoured bezlotoxumab.
Translating 180 day mortality to 15 day mortality	Applying flat 15 day mortality instead of higher rates in first 30 days	High (~70%). Favoured bezlotoxumab.
Application of mortality rate to patients with and without CDI recurrence	Applying data from Olsen 2015 directly rather than using the submission’s ‘target mortality’ approach applying an estimated relative risk to the probability of death reported for those without recurrence to estimate mortality in those with recurrence.	High (~35%). Favoured bezlotoxumab.
Number of bezlotoxumab doses per patient	Assuming one dose per recurrence rather than one dose in a life time (which was assumed by the submission).	High (~30%). Favoured bezlotoxumab.

Page numbers refer to sections of submission in which the claim of bias was made.

Source: constructed during evaluation using values presented in tables 3.9.1, 3.9.2 and 3.9.3 of the Commentary

6.38 Table 11 summarises the results of the stepped economic analysis, as discussed, these were re-estimated during the evaluation for the whole trial population, using the submission’s methodology.

**Table 11: Results from stepped economic analysis**

Parameter	Bezlotoxumab + SoC	SoC	Increment
<b>Step 1 Using whole trial results from MODIFY I and MODIFY II</b>			
Costs	\$ [redacted] <sup>1</sup>	\$0	\$ [redacted]
Outcomes (CDI recurrence rate)	[redacted] %	[redacted] %	[redacted] %
Cost per CDI recurrence avoided			\$ [redacted]
<b>Step 2 Results estimated using Markov model to determine life years</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Outcomes (life years)	5.3949	5.3186	0.0763
Cost per life year gained			\$ [redacted]
<b>Step 3 Apply utilities to Markov model to determine QALYs</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Outcomes (QALYs)	4.6065	4.5405	0.0660
Cost per QALY gained			\$ [redacted]

<sup>1</sup> calculated as cost of DPMQ of one vial of bezlotoxumab (\$ [redacted]) plus \$97.95 administration cost

Abbreviations: SoC=standard of care

Values above were corrected for transcriptional error in identifying proportion of hospitalisations for mild/moderate CDI.

Source: calculated using section 3 model.xlsm during evaluation

6.39 Results for the economic analysis updated for the high risk patient group, and corrected to account for the error in the estimated proportion of hospitalisations for mild/moderate CDI identified during the evaluation are provided in Table 12. This increased the ICER in the ‘high risk’ patients from \$15,000/QALY - \$45,000/QALY in the PSCR to \$15,000/QALY - \$45,000/QALY with the correction. The redacted table also shows the whole trial population resulted in an ICER of \$45,000/QALY – \$75,000/QALY.

**Table 12: Results of Modelled economic evaluation**

Population	Incremental cost	Incremental QALY	ICER <sup>^</sup>
Whole trial	\$ [redacted]	0.0660	\$ [redacted]
High risk	\$ [redacted]	0.0785	\$ [redacted]

<sup>^</sup> correcting for transcription error in the model for hospitalisation rate associate with mild/moderate CDI.

Source: Att 1\_ Zinplava Section 3\_revised spreadsheet and Section 3 model spreadsheet from submission

6.40 Overall, the biggest drivers of the model were the assumed differences in CDI recurrence and mortality between those treated with bezlotoxumab + SoC versus SoC alone.

6.41 There was no evidence of a significant difference in mortality between bezlotoxumab and placebo in the trials, the mortality rate in the trials were also much lower (7.6% and 7.1% in the placebo and bezlotoxumab arms at 84 days) versus those estimated in the model (15.4% and 14.8% in the placebo and bezlotoxumab arms). There was limited data from Australian sources to enable verification of the applied mortality data from Olsen 2015 which was derived for an US population. The ESC noted that in addition to the seemingly high mortality rate in the SoC group, Olsen *et al.* acknowledged the following limitations that are likely to have resulted in the overestimation of 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.

6.42 One Australian study (Huber *et al*, 2014) identified during the evaluation of a Department of Health surveillance snapshot of CDI across 175 hospitals during

2 months in Queensland in early 2012 suggested the numbers of death due to CDI may be lower in Australia. The study 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. A lower mortality due to CDI in Australia was also affirmed by a small west Australian study identified by the submission (Foster 2014) that estimated 30-day mortality to be 2.5% among hospitalised adult patients with CDI in two large teaching hospitals in Perth. Mitchel 2012 conducted a review of the mortality rates associated with CDI and concluded that all-cause mortality at 30 days could vary between 9% and 38% and is dependent on a range of risk factors including severity of CDI and age. It appeared the submission had applied the upper range of the values reported in the literature.

- 6.43 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.
- 6.44 There was also considerable variability in treatment effect of bezlotoxumab in prevention of CDI recurrence across different subpopulations (based on risk factor, see Table 5 above). If the PBS population should have lower risk for CDI recurrence, such as a greater proportion of patients with no CDI episodes in the last 6 months, the likely benefit associated with bezlotoxumab treatment will be lower than those estimated in overall trial results, resulting in a higher ICER. The ESC noted that the probability of recurrence in SoC arm in the trial and the model (26.6%) are higher than estimated using cross sectional Australian data (17.5%, assuming constant incidence of CDI over time). Furthermore, the ESC noted that the model probabilities were estimated using a complex formula and that it may be more appropriate to use the time to event data to estimate a hazard ratio for recurrent CDI to represent the effect of bezlotoxumab, which could be applied to the best available estimate of the probability of recurrent CDI in an Australian population.
- 6.45 The time horizon of the model also had a significant impact on the ICER. The submission argued that a 10 year model was appropriate to capture the long-term benefits of preventing CDI, however as noted above, given there was no clinical data beyond one year, a long time horizon would add considerably uncertainty to the modelled estimates. Based on the model presented, only the first 150 days out of the 3646 days of the model were informed by outcomes from the MODIFY I and MODIFY II trials. The ESC considered that if a mortality benefit is accepted, a 10-year time horizon may be reasonable to capture the longer-term benefits of reduced mortality. However, the ESC was of the view that the magnitude of the mortality benefit was overestimated. The PBAC noted that during the sponsor hearing, the presenting clinician indicated that there was a variation in the mortality rates globally. The clinician was also of the view that although Australian-specific mortality data was not very rigorous, mortality rates appeared lower in Australia compared to other countries, which may be associated with the lower incidence of the highly

virulent 027 ribotype. The PBAC therefore agreed with the ESC that the mortality rates were overestimated in the model.

- 6.46 The PBAC and ESC noted that the submission did not present analyses of repeat dosing, which appears to be likely in practice.
- 6.47 While the modelled economic evaluation (based on MODIFY I and MODIFY II) was consistent with the requested restriction, there were inconsistencies with the submission's proposed clinical management algorithm. For example, the model assumed patients will receive bezlotoxumab once only. While the PSCR proposed inclusion of a note in the restriction that PBS subsidy was for a single use in a patient's lifetime, the risk of additional use for subsequent recurrence, or new infections remained high. The pre-PBAC response argued that if a subsequent CDI were to occur within a patient's lifetime, the efficacy of bezlotoxumab in this repeat use would be expected to be the same, and it would therefore be reasonable to assume the same ICER. The PBAC considered that this assumption was incorrect because this assumes all subsequent recurrence or new infections occur more than 10 years after the initial use of bezlotoxumab, which was implausible. The PBAC also noted that a multivariate analysis using data from the whole trial population and assuming a time horizon of 5 years, allowing for repeat dosing in CDI recurrence and restricting use to severe CDI only (assuming 100% of patients enter model with severe CDI) yields an ICER of \$105,000/QALY – \$200,000/QALY compared to the base case of \$45,000/QALY – \$75,000/QALY, illustrating the sensitivity of the model to these assumptions.
- 6.48 The ESC noted that the model did not allow for sensitivity analysis on reduced mortality risk, reduced mortality RR, and reduced recurrent CDI risk, which would be informative.
- 6.49 The PBAC noted that the model did not take into account other important patient and health-system relevant benefits, such as a reduction in hospital bed days, which may be realised as a result of the reduction in CDI recurrence. The PBAC also noted that the sponsor hearing presented evidence that CDI had a considerable impact on quality of life, which is a relevant consideration.<sup>6</sup>

**Drug cost/patient/treatment: \$ [REDACTED]**

- 6.50 The average cost of bezlotoxumab was assumed to be \$ [REDACTED], based on the DPMQ (Private hospital) for 1 vial of 1,000mg and assuming 10% of the population will require two vials (i.e. weight >100kg but ≤200kg); and that patients will only use one dose per course of treatment. The cost for the comparator was \$0 because it was assumed that the cost for SoC is unchanged with bezlotoxumab treatment.

**Estimated PBS usage & financial implications**

- 6.51 This submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of CDI patients eligible for bezlotoxumab treatment. In its estimates, the submission assumed that bezlotoxumab will most

---

<sup>6</sup> Wilcox *et al.* 2017 "Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life" J Antimicrob Chemother. 72 (9): 2647-56.

likely be used where vancomycin is indicated (generally in severe or recurrent CDI), therefore the number of prescriptions required for bezlotoxumab was based on the number of PBS prescriptions for oral vancomycin (for CDI). The submission then assumed that the estimated number of patients using vancomycin would form 90% of the overall eligible population, with another 10% of the overall usage coming from use alongside metronidazole, maintaining a ratio of 1:9 metronidazole to vancomycin in each year of the financial estimates. This was likely an underestimate as the ratio of treatment with oral metronidazole to oral vancomycin based on the MODIFY I and MODIFY II was closer to 1:1. Assuming 1:1 metronidazole to vancomycin increased the cost to PBS considerably (see Table 14 below).

6.52 The submission did not account for administration costs associated with bezlotoxumab in its financial estimates. This cost was included during the evaluation and is presented in Table 13 below.

**Table 13: Summary of estimated financial impact and change in prescription numbers for listing bezlotoxumab**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Projected CDI episodes >18 years	█	█	█	█	█	█
Uptake rate of bezlotoxumab	20%	30%	40%	50%	50%	50%
Number of episodes which are assumed to be recurrence <sup>1</sup> without bezlotoxumab listing	█	█	█	█	█	█
Recurrence in patients treated with bezlotoxumab <sup>2</sup>	█	█	█	█	█	█
Recurrence in patients not treated with bezlotoxumab <sup>3</sup>	█	█	█	█	█	█
Remaining patients eligible for bezlotoxumab <sup>4</sup>	█	█	█	█	█	█
Estimated bezlotoxumab +vancomycin patients <sup>5</sup>	█	█	█	█	█	█
Estimated bezlotoxumab + metronidazole patients <sup>6</sup>	█	█	█	█	█	█
Estimated Bezlotoxumab vials used <sup>7</sup>	█	█	█	█	█	█
Net PBS/RPBS cost <sup>8</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Vancomycin treatments avoided <sup>9</sup>	█	█	█	█	█	█
Cost of vancomycin avoided <sup>10</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net change to PBS costs <sup>11</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net change to MBS costs <sup>12</sup>	\$ █ #	\$ █ #	\$ █ #	\$ █ #	\$ █ #	\$ █ #
Net change to government budget	\$ █ #	\$ █ #	\$ █ #	\$ █ #	\$ █ #	\$ █ #

<sup>1</sup> Assumed to be 34.0% of projected CDI episodes

<sup>2</sup> Assumed to be 22.3% of patients eligible for bezlotoxumab from previous year multiplied by uptake rate

<sup>3</sup> Assumed to be 34.0% of patients eligible for bezlotoxumab from previous year multiplied by (1- uptake rate)

<sup>4</sup> Estimated by total CDI episodes minus the theoretical number of CDI recurrences with no bezlotoxumab listing (34.0% of all CDI episodes in the previous year) with the expected recurrence in patients after bezlotoxumab listing.

<sup>5</sup> Estimated by uptake rate multiplied by remaining patients eligible for bezlotoxumab,

<sup>6</sup> Assume an additional 10% of patients will use metronidazole + bezlotoxumab based on vancomycin + bezlotoxumab estimate i.e. 10% metronidazole + bezlotoxumab and 90% vancomycin + bezlotoxumab

<sup>7</sup> Assumed that 10% of patients will require 2 vials

<sup>8</sup> Assume DPMQ \$ █ per vial, minus average copayment of \$16.49 for PBS and \$4.62 for RPBS

<sup>9</sup> Due to lower CDI recurrence. Difference between rate of CDI recurrence in patients treated with bezlotoxumab and not treated with bezlotoxumab (34.0%-22.3%) multiplied by the uptake rate of bezlotoxumab and projected CDI episodes > 18 years.

<sup>10</sup> Assume that 65% of all vancomycin scripts will be 125mg (DPMQ = \$260.25) and the remaining 35% will be 250mg (DPMQ = \$516.17) and an average copayment for vancomycin avoided for PBS is \$16.12 and RPBS is \$4.73

<sup>11</sup> Net cost of bezlotoxumab minus the cost of vancomycin avoided

<sup>12</sup> Estimated bezlotoxumab patients (+vancomycin or +metronidazole) multiplied by MBS item 14245 (\$97.95)

# indicates values added during evaluation.

Source: constructed during evaluation using Section 4 estimates.xlsx

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.53 The submission’s estimated uptake rates (20%, 30% and 40% in Years 1 to 3 and 50% in Year 4 and onward) were likely underestimates. Since bezlotoxumab is a novel drug with good tolerability and easy single dose, there would be little reason for eligible patients not to trial treatment. The submission also assumed that only one dose of bezlotoxumab will be given to each patient in a lifetime, this may not be appropriate given the requested restriction does not limit the number of times a patient can receive bezlotoxumab.

6.54 Results of the sensitivity analyses for the financial estimates are presented in Table 14.

**Table 14: Sensitivity analyses for the financial estimates**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
10% increase in CDI patients	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
5% decrease in annual uptake	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
20% increase in annual uptake	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
1:1 metronidazole: vancomycin (base case 1:9) <sup>1</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
bezlotoxumab given at each CDI episode (base case one dose per lifetime) <sup>2</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Recurrence rate as for whole trial population (base case: outpatients only)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

<sup>1</sup> Estimated by changing proportion of patient add-on to metronidazole from 10% to 50% (i.e. ratio of metronidazole + bezlotoxumab to vancomycin + bezlotoxumab is 1:1)

<sup>2</sup> 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 evaluation using Section 4 estimates.xlsx

The redacted table shows that at year 5, financial estimates were in the range of less than \$10 million per year and \$10 – \$20 million per year.

6.55 The PBAC noted DUSC’s advice that the estimates presented in the submission were likely to be underestimated because:

- The eligible population was likely an underestimate.
- The proposed place in therapy is for prevention, but that there was a risk that bezlotoxumab might be used as a treatment where there is unknown efficacy.
- Despite the increased rate applied in the PSCR, the uptake rates remain underestimated.

6.56 The PBAC further noted further advice from DUSC that:

- the listing of bezlotoxumab could change clinical practice and antibiotic prescribing patterns;
- in aged care facilities, there is risk of antibiotic resistance and concurrent use of other biologics, with unknown implications;

- faecal microbiota transplant 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.

6.57 Overall, the PBAC considered that submission's financial estimates were likely to be underestimated.

## Financial Management – Risk Sharing Arrangements

6.58 The sponsor indicated a willingness to enter a risk sharing arrangement with a cap/rebate structure to address uncertainty in utilisation. The PBAC considered that given the uncertainties in utilisation and high likelihood of repeat dosing for subsequent recurrence or new infection, a risk sharing arrangement would be required.

*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) recurrence in patients receiving antibiotic therapy for CDI on the basis of its modest effectiveness and uncertain incremental cost-effectiveness ratio (ICER).
- 7.2 The PBAC considered that the proposed restriction did not adequately define bezlotoxumab's place in therapy. 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, despite an indication in the restriction to limit use to once per patient lifetime.
- 7.3 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.
- 7.4 The PBAC considered that the nominated comparator, of placebo or standard of care antibiotics, was appropriate. However, 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.
- 7.5 The PBAC considered that the claim of superior efficacy over standard of care was supported by the data. However, the PBAC considered that whilst the observed efficacy was marginally better in the high risk sub-group, the overall benefit remained modest, and the clinical significance of such a benefit was unclear.
- 7.6 The PBAC considered that the claim of non-inferior comparative safety was not supported by the data when compared to oral antibiotics alone because in clinical practice patients not receiving bezlotoxumab will not have an infusion and will

therefore not be exposed to the risk of an infusion reaction. The PBAC considered that the total proportion of infusion reactions for bezlotoxumab, rather than the difference compared to placebo, was the more reasonable estimate of the adverse event rate.

- 7.7 The PBAC noted that there was no evidence of significant difference in mortality in the trials presented. The PBAC considered that the mortality rates and hence the mortality benefit for bezlotoxumab was considerably overestimated in the economic model. The PBAC noted that the mortality estimates were predicated on the assumption that the mortality rate in the USA and EU, was comparable to Australia, and that this assumption was not supported by published data or the views expressed by the clinician in the sponsor hearing. However, 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.
- 7.8 The PBAC did not agree with the sponsor's claim that repeat use for subsequent infection or recurrence would have the same incremental cost-effectiveness as single use, because this would rely on repeat use occurring more than 10 years (the model time horizon) after the initial dose, which was implausible. The PBAC considered that any future submission should address this appropriately.
- 7.9 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 advised that any future resubmission should be in the form of a major submission.
- 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 that access to Bezlotoxumab was not achieved for patients with recurrent C.Difficile infection in Australia. MSD will continue to work with the Department to make this therapy available as soon as possible.