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

1 Purpose of submission

1.1 The resubmission requested 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 antibiotics for CDI. This was the fourth submission for bezlotoxumab for prevention of CDI recurrence (see Previous PBAC consideration below).

1.2 As with the previous submissions, the key rationale for the PBS listing of bezlotoxumab was that there is currently no PBS listed treatments for the prevention of recurrent CDI and bezlotoxumab works via a novel mechanism of action. While there are no other drugs listed on the PBS to prevent recurrent CDIs, subsequent lines of antibiotic therapy are available for treatment of recurrent CDIs. In that sense, bezlotoxumab would delay or reduce the need for patients to access subsequent lines of antibiotics for treatment of CDI.

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

Table 1: Key components of the clinical issue addressed by the submission (as stated in the resubmission)

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

Abbreviations: CDI=clostridium difficile infection; IV=intravenous; SoC=standard of care
Underlined text refers to changes compared to previous submission in July 2019.
Shaded areas indicate unchanged from previous PBAC submission.
Source: Table 1-4, p11 of the resubmission.

2 Background

Registration status

2.1 The TGA approved bezlotoxumab on 8 November 2017 for prevention of recurrence of CDI in adult patients at high risk of recurrence. The current indication is:

"ZINPLAVA (bezlotoxumab) is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adult patients 18 years or older at high risk of recurrence of CDI who are receiving antibacterial therapy for CDI. ZINPLAVA is not indicated for the treatment of CDI. ZINPLAVA is not an antibacterial drug. ZINPLAVA should only be used in conjunction with antibacterial drug treatment of CDI."

Previous PBAC consideration

2.2 The PBAC rejected the previous submissions (November 2017, July 2018 and July 2019) on the basis of modest clinical benefit, concerns about safety, uncertain and unfavourable cost-effectiveness, uncertain financial estimates and high opportunity cost. The PBAC also considered that the previously proposed populations (i.e. ≥1 of 5 risk factors, ≥1 of 4 risk factors, and ≥2 of 4 risk factors) were poorly justified.

2.3 In July 2019, the PBAC reviewed the CDI recurrence rates in the placebo arm of the MODIFY trials to assess the prognostic value of each of the proposed risk factors, and noted that the treatment effect did not appear to be modified by three of the proposed risk factors including compromised immunity, clinically severe CDI and hypervirulent strain (paragraphs 6.14 and 6.15, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting). The PBAC considered that a future resubmission should restrict the proposed population to those aged ≥ 65 years and/or with a history of CDI in the past 6 months (i.e. ≥1 of 2 risk factors) (paragraph 7.9, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

2.4 The PBAC also considered in July 2019 that the cost-effectiveness should be informed by more reliable estimates of the risk of CDI recurrence, and the uncertainty associated with the assumed mortality benefit should be addressed. The PBAC advised that the uncertainty associated with the financial estimates would need to be addressed, including a risk sharing agreement with a 100% rebate over the financial caps (paragraph 7.9, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

2.5 Table 2 summarises key issues identified by the PBAC in the previous submissions and how this resubmission addressed them.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Proposed population	The PBAC considered that the requested population was poorly justified clinically and epidemiologically (Para 7.2, July 2019 PSD).	Addressed in the resubmission; PBS population also included a third new risk factor for transplant recipients.
	The PBAC considered that any future resubmission should restrict the proposed PBS population to those aged ≥65 years and/or with a history of CDI in the past 6 months.	
Cardiac failure serious adverse events	The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data provided in the resubmission as the possibility of an increased risk of exacerbation of CHF remained (Para 7.5, July 2019 PSD).	Not addressed given there was no new data available.
CDI recurrence rates	The PBAC noted the base case ICER in the resubmission was highly sensitive to the assumed CDI recurrence rates (Para 7.6, July 2019 PSD); and should be informed by more reliable estimates of the risk of CDI recurrence.	Revised CDI recurrence rates provided; the model remained highly sensitive to the assumed CDI recurrence rates.
	ESC considered that an option for the estimation of SoC recurrence rates may be to use the reported difference in recurrence rates by risk factor to estimate recurrence rates from the aggregate recurrence rate cited by the ACSQHC (Para 6.34, July 2019 PSD).	
Financial estimates	The PBAC had previously considered that the financial estimates were highly uncertain and likely an underestimate for several reasons including the derivation of the eligible population from oral vancomycin scripts on the PBS, which only accounted for approximately 10% of CDI related diarrhoeas (Para 6.49, July 2019 PSD).	Addressed in the resubmission by estimating the eligible population from hospital admissions.
Risk sharing arrangement	The PBAC advised that the uncertainty associated with the financial estimates would need to be addressed, including with a risk sharing arrangement with a 100% rebate over the financial caps (Para 7.9, July 2019 PSD).	Partially addressed; the resubmission proposed a risk sharing arrangement but provided limited detail.

Abbreviations: ACSQHC=Australian Commission on Safety and Quality in Health Care; CDI=clostridium difficile infection; CHF=congestive heart failure.
Source: constructed during the evaluation.

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

3 Requested listing

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

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BEZLOTOXUMAB Concentrated vial for injection 1g/40 mL, 40 mL vial	1	1	0	published prices $4,365.00 (public) $4,412.02 (private) effective price $[redacted] (public) $[redacted] (private)	Zinplava®	Merck Sharp & Dohme (Australia) Pty Ltd

Concept ID	**Category / Program:** Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: **[ ]** Unrestricted benefit [ ] Restricted benefit ~~[X] Authority Required – In Writing~~ [X] Authority Required – Telephone/Electronic/Emergency [ ] Authority Required - Streamlined
	Condition: *Clostridium difficile infection*
new	**Indication:** Clostridium difficile infection
	Treatment phase: ~~Initial~~
	Clinical criteria:
24235 draft	Patients must have confirmed toxin B positive Clostridium difficile infection
	AND
new	**Clinical criteria:**
new	Patient must be at high risk of recurrence, defined as having one or more risk factors for Clostridium difficile infection recurrence.
	AND
	Treatment criteria:
24237 draft	Patients must be receiving antibacterial therapy for Clostridium difficile infection.
new	**Prescriber Instructions:** High risk is defined by the presence of one or more of the following factors: *(i)* age 65 years or older; *(ii)* history of Clostridium difficile infection in the past 6 months; *(iii)* immunocompromised due to history of haematopoietic stem cell transplant or solid organ transplant.
24240 draft	**Prescriber Instructions:** The medical practitioner should request sufficient quantity based on the weight of the patient to provide for a dose of 10 mg per kg.
24241 draft	**Administrative Advice:** Repeat ~~administration~~ *authority requests* ~~is~~ *will* not *be* ~~permitted~~ *authorised* within 90 days of ~~the initial episode.~~ *a previous supply*
7608	**Administrative Advice:** *Special Pricing Arrangements apply.*

3.2 Compared with July 2019 submission, the resubmission proposed a lower effective DPMQ (via special pricing arrangement) for bezlotoxumab of $[redacted] (public hospitals) but maintained the published price of $4,365. The effective price is [redacted]% lower compared to the previous resubmission in July 2019 and [redacted]% lower compared to the first submission in November 2017.

3.3 The resubmission requested a revised Section 100 Authority Required listing for bezlotoxumab compared to the previous resubmission in July 2019. The resubmission proposed a new definition of high risk of CDI recurrence as ≥1 of 3 risk factors, which included two risk factors recommended by the PBAC (age ≥65 years, or history of CDI in the past 6 months), and a third new risk factor proposed by the Sponsor (immunocompromised due to history of haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)).

Table 3: Definition of high-risk population for treatment with bezlotoxumab in the current and previous resubmissions

Resubmission July 2019	Current resubmission
Defined as ≥2 of 4 risk factors:	Defined as ≥1 of 3 risk factors
- Age ≥ 65 years	- Age ≥ 65 years
- History of CDI in past 6 months	- History of CDI in past 6 months
- Immunocompromised[a]	- Immunocompromised due to history of haematopoietic stem cell or solid organ transplant
- Clinically severe CDI[b]	

Shaded areas indicate information previously seen by the PBAC
Abbreviations: CDI=clostridium difficile infection.
[a] Patients with compromised immunity, including patients receiving immunosuppressive therapy or with an illness associated with immunosuppression.
[b] Severe infection defined as a ZAR score of 2 or higher.
Source: Table 1.4.3 of July 2019 resubmission and constructed during the evaluation.

3.4 Extending PBS listing to transplant patients was based on the following (see Table 4 for supporting evidence):

- Patients with HSCT or SOT experience high rates of CDI and risk of recurrence;
- A high proportion of patients with HSCT or SOT will be ineligible for treatment under the eligibility criteria proposed by the PBAC;
- Patients with HSCT or SOT have fewer alternative therapies because they may not be suitable for faecal microbiota transplant; and
- The financial impact of extending listing to patients with HSCT or SOT is limited, corresponding to approximately 600 patients per year.

Table 4: Key arguments and supportive evidence presented in the resubmission for extending listing to immunocompromised patients with HSCT or SOT

Patients with HSCT or SOT experience high rates of CDI and risk of recurrence	- A prospective study (Schuster et al 2017) of HSCT recipients in four US transplant centres from 2006-2011 (N=444) found that CDI was the most common bacterial pathogen causing infection. Approximately 33% of patients developed a CDI, of which 74% had a single episode and 26% developed recurrent CDI. Approximately 63% of patients who developed CDI died during the follow-up period compared to 47% without CDI infection. - A retrospective review (Ilett et al 2019) of HSCT (N=573) and SOT (N=1114) recipients in Denmark from 2010-2017 found that that 20% of HSCT recipients and 15% of SOT recipients developed CDI post-transplant. The highest rates of CDI occur in the first month post-transplant, and was more common in those undergoing liver and lung compared to kidney and heart transplants. - A meta-analysis (Paudel et al 2015) of 30 studies (N=21,683) from 1991-2014 reported a CDI prevalence rate of 7.4% among SOT patients from the time of transplant to first discharge from hospital, ranging from 3.2% for pancreas transplants to 10.8% for lung transplants. The reported CDI recurrence rate based on 15 studies was estimated to be 19.7%.
A high proportion of patients with HSCT or SOT will be ineligible for treatment under the eligibility criteria proposed by the PBAC.	- Data from the Australasian Bone Marrow Transplant Recipient Registry indicated 77-80% of HSCT recipients in 2015-2017 were < 65 years of age. - The median age was 52-53 years in the retrospective review of HSCT and SOT patients in Denmark (Ilett et al 2019) and prospective study of HSCT recipients in US transplant centres (Schuster et al 2017).
Patients with HSCT or SOT have fewer alternative therapies.	- New therapies emerging for the treatment of CDI such as faecal microbiota transplant are unlikely to be suitable for haematologic patients with neutropenia and/or HSCT patients (Oksi et al 2019).
The financial impact of extending listing to patients with HSCT or SOT was limited.	- The resubmission also noted that only those < 65 years would be additional to patients eligible under the other two risk factors (≥65; history of CDI) with 78%-80% of HSCT patients < 65 years from Australasian Bone Marrow Transplant Recipient Registry data. - The 2018 Australian Donation and Transplantation Activity Report stated there were 1,544 SOT recipients in 2018. The resubmission (p87) noted that approximately 15% of SOT recipients would develop CDI, presumably based on Ilett et al 2019. - Australasian Bone Marrow Transplant Recipient Registry data indicated 1700 patients undergoing HSCT each year in 2015-2017 (Appendix 5 of the resubmission). Based on Schuster et al 2017, approximately one-third of patients with HSCT will experience CDI. Alternatively based on Ilett et al 2019, 20% of patients with HSCT will develop CDI.

Abbreviations: CDI=clostridium difficile infection; HSCT= haematopoietic stem cell transplant; SOT = solid organ transplant, US = United States.
Source: pp.86-87 of the resubmission.

3.5 The resubmission did not present any clinical trial data to inform the treatment effect of bezlotoxumab for an immunocompromised population with HSCT or SOT. The ESC considered it plausible for there to be differences in the comparative effectiveness and safety of bezlotoxumab between the proposed immunocompromised population and that reported in the MODIFY trials for patients with ≥1 of 2 risk factors (age ≥65 years, or history of CDI in the past 6 months).

3.6 The revised restriction continued to permit patients to undergo repeat administration of bezlotoxumab 90 days after the initial episode. The PBAC had previously considered

it was probably and likely appropriate that bezlotoxumab be used more than once within a patient's lifetime, but in the absence of evidence also considered it may be more appropriate to limit use to one dose per lifetime in the restriction (paragraph 2.3, bezlotoxumab, Public Summary Document, July 2018 PBAC meeting). The resubmission did not present any new clinical or economic evidence to support repeat dosing with bezlotoxumab, and did not account for potential uncertainty with repeat dosing. A recent Australian study (Alfayyadh et al 2019) indicated that 64% of recurrent CDIs were relapsed infections (i.e. the same ribotype) and 36% were re-infections (i.e. a different ribotype). The Pre-Sub-Committee Response (PSCR) stated that feedback from experts indicated that they are unlikely to use bezlotoxumab twice in a patient who experiences a recurrence after receiving bezlotoxumab. Further, the sponsor considered such patients may be candidates for alternative therapeutic options such as faecal microbiota transplant.

3.7 The product information (PI) recommends that bezlotoxumab (10mg/kg as a single dose intravenous infusion over 60 minutes) is administered concurrently with antibiotics for treatment of CDI. Patients admitted to hospital for CDI will only be eligible for PBS funded bezlotoxumab on the day of discharge. The timing of administration relative to the start of antibiotics for treatment of CDI did not impact on effectiveness in the MODIFY trials. Approximately 94% of patients received bezlotoxumab within 6 days of CDI confirmation in the trials, which is consistent with average length of stay in Australia for patients with a principal diagnosis of gastroenterocolitis caused by CDI (7.8 days).

3.8 The resubmission implicitly assumed that the proposed Section 100 listing (public and private hospitals) of bezlotoxumab will not change prescribing behaviour including the treatment setting. Specifically, that the same proportion of patients will be treated for CDI in hospital and the community (e.g. nursing homes) before and after PBS listing of bezlotoxumab. It was unclear whether some prescribers may subsequently refer community patients to hospitals in order to receive treatment with bezlotoxumab on the PBS. The PSCR stated that as bezlotoxumab is a Section 100 drug requiring infusion it is unlikely to be used extensively in mild/moderate cases of CDI that are treated outside a hospital setting. The ESC noted that the results of the 2015 Aged Care National Antimicrobial Prescribing Survey[1] (AC-NAPS) indicate that treatment of CDI appears to be uncommon in Australian nursing homes. However, the ESC considered that the overall prevalence of Australian community treatment of CDI was not known and may differ from the MODIFY trials (80% of high risk subgroup were inpatients).

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

[1] National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing and infections in Australian residential aged care facilities: Results of the 2015 Aged Care National Antimicrobial Prescribing Survey pilot. Sydney: ACSQHC, 2016.

4 Population and disease

4.1 *Clostridium difficile* is a bacteria widely distributed in the environment and faecal flora of humans and animals. Infection occurs following disruption of the normal gut flora (commonly due to antibiotic use) and acquisition of the bacteria typically via the faecal-oral route. Toxin producing strains of *Clostridium difficile* cause disease, with symptoms including watery diarrhoea, fever, nausea and abdominal pain. CDI recurrence can be due to persistent or newly-acquired *Clostridium difficile* spores. Subsequent gut flora disturbance caused by antibiotics can lead to spore outgrowth and new toxin expression.

4.2 Bezlotoxumab is a human monoclonal antibody that binds with high affinity to *Clostridium 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.

4.3 The PBAC noted the clinical management algorithm was based on the Australasian Society of Infectious Diseases *Guidelines for the management of CDI in adults and children in Australia and New Zealand* (Trubiano et al, 2016). The PBAC noted the proposed clinical management algorithm was unchanged from the July 2019 resubmission, indicating that patients at 'high risk' (undefined) of CDI recurrence will be administered bezlotoxumab as add-on to antibiotic therapy for both initial and recurrent CDIs (non-severe and severe episodes). The PBAC noted that the 2016 guidelines recommended faecal microbiota transplantation as a therapeutic option for second or subsequent CDI recurrence (non-severe and severe episodes) if therapy with vancomycin or fidaxomicin had failed and no contraindications.[2] The PBAC noted the publication of the *Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice* in 2020.[3] The PBAC noted the consensus statements recommend antibiotics as first-line therapy for an initial episode of CDI with evidence for this statement rated as high according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool and the strength of evidence rated as strong. The PBAC noted that faecal microbiota transplantation is recommended for patients with recurrent CDI with evidence for this statement rated as high according to the GRADE tool and the strength of the evidence rated as strong. The PBAC considered that the 2020 Australian consensus statements

[2] Trubiano JA, et al. Australasian Society of Infectious Diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand. Intern Med J 2016;46:479-93

[3] Haifer C, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice Gut 2020;**0**:1–10. doi:10.1136/gutjnl-2019-320260

confirm a shift in the clinical management algorithm for CDI with a preference for the use of faecal microbiota transplantation in the treatment of recurrence.

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

5 Comparator

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

5.2 The PBAC considered that, with the recent shift in the clinical management algorithm outline above (see paragraph 4.3), SoC antibacterial therapy alone does not accurately reflect current clinical practice where faecal microbiota transplantation is a preferred treatment option for CDI recurrence.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

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

Clinical trials

6.3 The resubmission was based on the same trials as the previous submissions: two head-to-head randomised trials comparing bezlotoxumab to placebo (MODIFY I and MODIFY II). The resubmission presented new data for a *post-hoc* subgroup of patients with ≥1 of 2 risk factors (age ≥65, history of CDI in past 6 months), which was conducted for this resubmission. The ESC considered that the use of the post-hoc subgroup of patients with ≥1 of 2 risk factors reduced the sample size significantly and increased the potential for selection bias.

6.4 The resubmission stated that there was no data in the MODIFY trials specific to immunocompromised patients due to HSCT or SOT. The "immunocompromised" subgroup in the trials refers to a broad range of immunocompromised patients on the basis of their medical history or use of immunosuppressive therapy. Available data indicated only 18 patients had received a stem cell transplant and history of organ transplant was unknown.

6.5 Approximately one third of patients enrolled in the MODIFY trials (N=520/1554) had toxin B positive CDI and met the revised risk criteria (i.e. ≥1 of 2 risk factors). The ESC noted that several baseline characteristics were not balanced between arms in the post-hoc subgroup, with patients treated with bezlotoxumab being more likely to be male (45% vs 38%), treated as an inpatient (84% vs 77%), weigh >100kg (6% vs 3%) and have no CDI in the past 6 months (63% vs 57%) compared to placebo.

6.6 Table 5 provides the trials and associated reports presented in the resubmission.

Table 5: Trials and associated reports presented in the resubmission

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

Shaded areas indicate data previously seen by the PBAC.
Note: only main trial citations have been included in this table.
Source: p43 of the resubmission.

Comparative effectiveness

6.7 Table 6 summarises the main efficacy outcomes in the MODIFY trials for the requested populations in the current (≥1 of 2 risk factors only) and previous submissions. The main outcome relied on by the resubmission for its clinical claim was CDI recurrence (primary outcome), and the minimal clinically important difference (MCID) was the reduction in recurrence of 8-9%, unchanged from the previous submissions. The PBAC previously considered that global cure was a more relevant endpoint as it is 'more interpretable', since clinically, the goal would be to get cured, stay alive, and remain free of recurrent infection over time (paragraph 6.8; bezlotoxumab, Public Summary Document, November 2017 PBAC meeting).

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

Population	Bezlotoxumab n/N (%)	Placebo n/N (%)	Risk difference % (95% CI)[a]	Relative Risk (95% CI)[#]
CDI recurrence at 12 weeks				
November 2017 submission:				
- All patients	129/781 (16.5)	206/773 (26.6)	**-10.0 (-14.0, -6.0)^**	**0.62 (0.51,0.75)**
July 2018 resubmission (clinical):				
- ≥1 of 5 risk factors[b]	100/592 (16.9)	174/583 (29.8)	**-12.8 (-17.6, -8.0)**	**0.57 (0.46, 0.71)**
- Complement	29/189 (15.3)	32/190 (16.8)	-1.5 (-9.0, 6.0)	0.91 (0.58, 1.44)
July 2018 resubmission (model):				
- ≥1 of 4 risk factors[c]	97/581 (16.7)	167/562 (29.7)	**-13.0 (-17.9, -8.2)**	**0.56 (0.45, 0.70)**
- Complement	NR	NR	NR	NR
July 2019 resubmission:				
- ≥2 of 4 risk factors[c] (& toxin B pos.)	24/146 (16.4)	51/150 (34.0)	**-16.8 (-26.7, -6.9)[d]**	**0.48 (0.32, 0.74)****
- Complement (& toxin B pos.)	31/236 (13.1)	56/241 (23.2)	**-10.2 (-17.2, -3.3)[d]**	**0.57 (0.38, 0.84)**
March 2020 resubmission:				
- ≥1 of 2 risk factors[f] (& toxin B pos.)	41/254 (16.1)	86/266 (32.3)	**-15.6 (-22.9, -8.3)[d]**	**0.50 (0.36, 0.69)****
- Complement (& toxin B pos.)	14/128 (10.9)	21/125 (16.8)	-5.6 (-14.8, 3.3)[d]	0.65 (0.35, 1.22)**
CDI recurrence in patients who attained clinical cure of initial episode at 12 weeks				
November 2017 submission:				
- All patients	129/625 (20.6)	206/621 (33.2)	**-12.2 (-17.1, -7.4)^**	**0.62 (0.51, 0.75)**
July 2018 resubmission:				
- ≥1 of 5 risk factors[b]	100/471 (21.2)	174/468 (37.2)	**-15.9 (-21.6, -10.2)**	**0.57 (0.46, 0.70)**
- Complement*	29/154 (18.8)	32/153 (20.9)	-2.1 (-11.1, 6.9)	0.90 (0.58, 1.41)
July 2019 resubmission:				
- ≥2 of 4 risk factors[c] (& toxin B pos.)	24/113 (21.2)	51/122 (41.8)	**-19.2 (-30.8, -7.2)[d]**	**0.51 (0.34, 0.77)****
- Complement (& toxin B pos.)	31/199 (15.6)	56/202 (27.7)	**-11.2 (-19.3, -3.2)**	**0.56 (0.38, 0.83)**
March 2020 resubmission:				
- ≥1 of 2 risk factors[f] (& toxin B pos.)	41/207 (19.8)	86/221 (38.9)	**-18.3 (-26.7, -9.7)[d]**	**0.51 (0.37, 0.70)****
- Complement (& toxin B pos.)	14/105 (13.3)	21/103 (20.4)	-6.3 (-17.1, 4.3)[d]	0.65 (0.35, 1.21)**
Global cure at 12 weeks (clinical cure of initial episode and no CDI recurrence)				
November 2017 submission:				
- All patients	496/781 (63.5)	415/773 (53.7)	**9.7 (4.8, 14.5)^**	**1.18 (1.09, 1.29)**
July 2018 resubmission:				
- ≥1 of 5 risk factors[b]	371/592 (62.7)	294/583 (50.4)	**12.1 (6.4, 17.7)**	**1.24 (1.12, 1.37)**
- Complement	125/189 (66.1)	121/190 (63.7)	2.8(-6.9, 17.7)	1.04 (0.9, 1.21)
July 2019 resubmission:				
- ≥2 of 4 risk factors[c] (& toxin B pos.)	89/146 (61.0)	71/150 (47.3)	**12.6 (1.1, 23.9)[d]**	**1.29 (1.04, 1.59)****
- Complement (& toxin B pos.)	168/236 (71.2)	146/241 (60.6)	**10.5 (1.9, 18.8)**	**1.18 (1.03, 1.34)**
March 2020 resubmission:				
- ≥1 of 2 risk factors[f] (& toxin B pos.)	166/254 (65.4)	135/266 (50.8)	**13.7 (5.2, 22.1)[d]**	**1.29 (1.11, 1.49)****
- Complement (& toxin B pos.)	91/128 (71.1)	82/125 (65.6)	4.8 (-7.12, 16.5)[d]	1.08 (0.92, 1.28)**

Shaded areas indicate data previously seen by the PBAC. **Bold** indicates statistical significant results.

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

Not adjusted for stratification factors

* From Gerding et al 2018.

** Indicates values calculated during evaluation using StatsDirect

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

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

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

[d] Based on the Miettinen and Nurminen method stratified by protocol (MODIFY I vs MODIFY II) and SoC therapy.

f Including: Age ≥65 years, ≥1 CDI episode in past 6 months.

Source: Tables 2-42 to 2-46, pp96-98- of the resubmission; *and constructed during the evaluation.*

6.8 Consistent with the previous submissions, there were fewer CDI recurrences at Week 12 in patients treated with bezlotoxumab versus placebo for the requested population, toxin B positive patients with ≥ 1 of 2 risk factors. Similar results were reported for the other outcomes (CDI in patients who attained clinical cure of the initial episode, and proportion of patients who achieved global cure) in favour of bezlotoxumab. The ESC noted the relative treatment effect was greater for the proposed high risk subgroup (RR=0.50) compared with the complement group (RR=0.65) however, a statistical interaction test for treatment effect variation by risk status was not undertaken and thus it is unclear if the relative efficacy of bezlotoxumab is greater in the high risk population. The ESC further noted the relative efficacy from the subgroup (RR=0.50) was utilised in the economic model.

6.9 Unlike the July 2019 resubmission, the estimated treatment effect for CDI recurrence at Week 12 in toxin B positive patients with ≥1 of 2 risk factors met the nominated MCID (i.e. the upper 95%CI was larger than -8%). The ESC noted the unmatched baselined characteristics (including gender, treatment setting, weight and history of CDI) in the post-hoc subgroup and considered that this introduced uncertainty in the estimated treatment effect reported. Results for the complement population (i.e. toxin B positive patients with 0 of 2 risk factors) showed no significant differences for any of the key outcomes for patients treated with bezlotoxumab compared to placebo.

6.10 The PBAC recalled that there was no evidence of a reduction in mortality associated with bezlotoxumab based on the results of the MODIFY trials (paragraph 6.16, bezlotoxumab Public Summary Document, July 2019 PBAC meeting, paragraph 7.4, bezlotoxumab Public Summary Document, July 2018 PBAC meeting).

6.11 The resubmission identified two small real world studies of bezlotoxumab:

- Kerr et al 2019 conducted a retrospective study of 21 patients with a SOT and treated for CDI at a medical centre in the United States. Patients received antibiotics with bezlotoxumab (N=9) or without bezlotoxumab (N=12) at physician discretion. The 90-day recurrence rates were 9% (n=1) and 33% (n=3) with and without bezlotoxumab, respectively. The study results were not informative given treatment was not random or random-like and baseline characteristics (including risk factors for CDI recurrence) were not balanced across the comparison groups.
- Oksi et al 2019 conducted a retrospective study of 46 patients treated with bezlotoxumab for CDI in Finland. Approximately 27% of patients had CDI recurrence after 3 months. The proportion of patients with recurrent CDI was higher in this study compared to the treatment arm in the MODIFY trials (16.5% for ITT population). The population in Oksi et al., 2019 appeared to have more risk factors than those in MODIFY (average age ~65 years compared to ~63 years, 61% immunocompromised compared to 20%, 37% severe CDI compared to 16%).

Comparative harms

6.12 The resubmission presented a summary of adverse events (AEs) for the subgroup of patients with ≥1 of 2 risk factors (age ≥ 65 years; history of CDI in past 6 months) in the MODIFY trials (Table 7) and reasonably concluded that the overall AEs and SAEs were similar between treatment arms. The results were consistent with the overall population.

6.13 Approximately 10% of bezlotoxumab patients reported infusion specific AEs, including nausea (3%), headache (2%), dizziness (1%), fatigue (1%) and pyrexia (1%).

Table 7: Summary of Treatment Related adverse events in the subpopulation with ≥1 of 2 risk factors (age ≥ 65 years; history of CDI in the past 6 month) in MODIFY-I and MODIFY II trials at Week 12 post infusion

Adverse events (AE)	Bezlotoxumab N=253, n (%)	Placebo N=268, n (%)	Risk Difference (95% CI)*	Relative risk (95% CI)*
one or more AE	172 (68.0)	188 (70.1)	-2% (-10%, 6%)	0.97 (0.86, 1.09)
drug-related AE	24 (9.5)	15 (5.6)	4% (-1%, 8%)	1.69 (0.91, 3.16)
serious AE	90 (35.6)	103 (38.4)	-3% (-11%, 5%)	0.93 (0.74, 1.16)
serious drug-related AE	3 (1.2)	1 (0.4)	1% (-1%, 2%)	3.18 (0.33, 30.35)
Death	28 (11.1)	24 (9.0)	2% (-3%, 7%)	1.24 (0.74, 2.07)
discontinued due to an AE	0	0	-	-

*Indicates values calculated during evaluation using RevManv5.3.
Source: Table 2-48, p100 of the resubmission.

6.14 The resubmission did not present any new data on the risk of exacerbation of congestive heart failure (CHF) with bezlotoxumab, and reiterated arguments that there were confounding factors that could explain the higher incidence of heart failure for patients with CHF (Table 8). The PBAC had previously noted that there was a higher incidence of heart failure in bezlotoxumab treated patients compared to placebo, and amongst those with a history of heart failure, there was a higher incidence of acute heart failure and of mortality in participants treated with bezlotoxumab than those treated with placebo (paragraph 7.3, bezlotoxumab, Public Summary Document, July 2018 PBAC meeting).

Table 8: Summary of adverse events in the subgroup of patients with a history of congestive heart failure (CHF) at baseline in MODIFY I and MODIFY II at Week 12

Adverse events (AE)	Bezlotoxumab N=118, n (%)	Placebo N=104, n (%)	Risk Difference (95% CI)*	Relative risk (95% CI)*
One or more AE	99 (83.9%)	73 (70.2%)	**14% (3%, 25%)**	**1.20 (1.03, 1.39)**
Drug-related AE	9 (7.6%)	5 (4.8%)	3% (-3%, 9%)	1.59 (0.55, 4.58)
Serious AE	63 (53.4%)	50 (48.1%)	5% (-8%, 18%)	1.11 (0.86, 1.44)
Cardiac SAE	21 (17.8%)	9 (8.7%)	9% (0%, 18%)	2.06 (0.99, 4.29)
Cardiac failure SAE	*15[a] (12.7%)*	*5 (4.8%)*	**8% (1%, 15%)**	2.64 (1.00, 7.03)
Deaths	23 (19.5%)	13 (12.5%)	7% (-3%, 13%)	1.56 (0.83, 2.92)
Cardiac deaths	9 (7.6%)	5 (4.8%)	3% (-3%, 9%)	1.60 (0.55, 4.63)

Text in bold indicate statistical significance.
* Indicates values calculated during evaluation using RevManv5.3
[a] Included one patient on bezlotoxumab with cardiopulmonary failure
Source: based on Tables 2-7, Congestive heart failure adverse event attachment submitted with the July 2019 resubmission.

6.15 The July 2019 resubmission stated that an association between bezlotoxumab and exacerbation of CHF has not been determined. There was no evidence of preclinical cardiac toxicity, the trials did not include CHF as a stratification factor and investigators did not collect information on CHF classification. The subset of patients with CHF at baseline included older patients with more comorbid conditions than the overall trial population, and there were imbalances in baseline characteristics across the arms. The observed difference in the number of deaths was not due to cardiac deaths. The ESC reiterated its July 2019 advice that the signal for possible exacerbation of CHF remained, and that further data is required to evaluate this risk (paragraph 6.20, bezlotoxumab, Public Summary Document, July 2018 PBAC meeting).

Benefits/harms

6.16 A summary of the comparative benefits and harms for bezlotoxumab plus SoC versus SoC alone is presented in Table 9.

Table 9: Summary of comparative benefits and harms for bezlotoxumab and SoC in the trials (total trial populations and high-risk subgroups) – Pooled data from MODIFY-I and MODIFY II trials

Benefits						
CDI recurrence at 12 weeks						
Trial	**Bez + SoC**	**SoC**	**RR (95% CI)**	**Events/100 patients[a]**		**RD (95% CI)**
				Bez + SoC	**SoC**	
≥1 of 2 risk factors (≥65; CDI history)	41/254	86/266	**0.50 (0.36, 0.69)***	16.1	32.3	**-15.6 (-22.9, -8.3)**
Global cure at 12 weeks						
≥1 of 2 risk factors (≥65; CDI history)	166/254	135/266	**1.29 (1.11, 1.49)***	65.4	50.8	**13.7 (5.2, 22.1)**
Harms						
	Bez + SoC	**SoC**	**RR (95% CI)**	**Events/100 patients[a]**		**RD (95% CI)**
				Bez + SoC	**SoC**	
Infusion specific adverse events (e.g. nausea, dizziness, headache, fatigue and pyrexia)						
Total population	81/786 (10)	0/781[a]	**162.0 (21,NA)**	10.3	0	**10.0 (8.3,12.6)**

Shaded areas indicate data previously seen by the PBAC.

* Indicates values calculated during evaluation using RevMan v5.3t.

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

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

Source: constructed during the evaluation.

6.17 On the basis of direct evidence presented by the resubmission, for every 100 patients in a post-hoc analysis of a sub-group with ≥ 1 of 2 risk factors treated with bezlotoxumab plus SoC in comparison with SoC:

- Approximately 16 fewer patients would have CDI recurrence at 12 weeks.
- Approximately 14 additional patients would have global cure at 12 weeks.

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

- Approximately 10 additional patients would experience an infusion specific adverse event and there may be a possible increase in risk of heart failure.

Clinical claim

6.18 The resubmission described bezlotoxumab with SoC as superior in terms of effectiveness compared with SoC and non-inferior in terms of safety compared to SoC, for patients with ≥ 1 of 2 risk factors (age ≥ 65 years; history of CDI in past 6 months); the resubmission did not make a clinical claim for immunocompromised patients due to history of HSCT or SOT. The claim of superior effectiveness and non-inferior safety was unchanged from the previous submissions in reference to different populations.

6.19 In terms of comparative effectiveness, the data presented in the resubmission supported the claim of superior effectiveness for patients with ≥1 of 2 risk factors. The PBAC had previously considered that the MODIFY trials supported the claim of superior effectiveness for the previous populations but the overall benefit was modest and clinical significance was unclear (paragraph 7.5, bezlotoxumab, Public Summary Document, November 2017 PBAC meeting; paragraph 7.2, bezlotoxumab, Public Summary Document, July 2018 PBAC meeting; paragraph 6.28, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting). The ESC agreed with the evaluation that the data presented in the resubmission supported the claim of superior effectiveness for patients with ≥1 of 2 risk factors.

6.20 In terms of comparative safety, the data presented in the current resubmission again did not support the claim of non-inferior safety for patients with ≥1 of 2 risk factors. The PBAC had previously considered:

- that a claim of inferior comparative safety would be more reasonable … because SoC does not require an infusion, patients treated with bezlotoxumab may suffer additional infusion related adverse events (paragraph 6.27, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting); and
- that the claim of non-inferior comparative safety was not adequately supported given the possibility of an increased risk of exacerbation of CHF with bezlotoxumab (paragraph 7.5, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

The ESC reiterated its July 2019 advice that a claim of inferior comparative safety may be more reasonable due to the reported proportion of bezlotoxumab treated patients who experienced infusion specific AEs (10%) and ongoing concerns regarding a signal for possible exacerbation of CHF (paragraph 6.27, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

6.21 The PBAC considered that the claim of superior comparative effectiveness was reasonable for patients with ≥ 1 of 2 risk factors. However, the PBAC reiterated its previous advice that the overall benefit remained modest and the clinical relevance of the benefit unclear.

6.22 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.23 The structure of the modelled economic evaluation remained unchanged from previous submissions; however, the resubmission updated model inputs including the assumed CDI recurrence rate for SoC, population characteristics for the revised high risk population, and price per vial of bezlotoxumab. The ESC noted that while patients immunocompromised due to a history of HSCT or SOT were included in the revised high risk population, they were not specifically included in the economic model.

6.24 In July 2018 and in reference to patients with ≥1 of 4 or 5 risk factors, the PBAC considered that the most informative analysis for decision making was to apply the following parameters (paragraph 7.6; bezlotoxumab, Public Summary Document, July 2018 PBAC meeting):

- 10-year time horizon;
- Hazard ratio (HR) for mortality due to CDI 1.12;
- 2.5% mortality without CDI recurrence;
- Hospitalisation costs as per AR-DRG (i.e. unadjusted for length of stay); and
- 17.5% CDI recurrence for SoC and 9.8% for bezlotoxumab.

6.25 The resubmission (and the July 2019 resubmission) adopted most of the parameters recommended by the PBAC with the exception of the CDI recurrence rates. The PBAC had recommended that the model apply a lower rate of CDI recurrence than the trial because the generalisability of the trial population to the Australian population was uncertain and available data suggested that the risk of recurrence in Australia may be lower than the MODIFY trials (paragraph 6.16, bezlotoxumab, Public Summary Document, November 2017 PBAC meeting).

6.26 In July 2019, the Sponsor argued that the 17.5% CDI recurrence rate for SoC (reported in Foster et al 2014) was not reasonable or applicable to the patients with ≥2 of 4 risk factors for several reasons, and again applied the higher trial-based rates. The ESC agreed with the Sponsor and considered that an appropriate CDI recurrence rate for SoC for an Australian high risk population may be higher than the 17.5% proposed by the PBAC in July 2018 (paragraphs 6.33 and 6.34, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

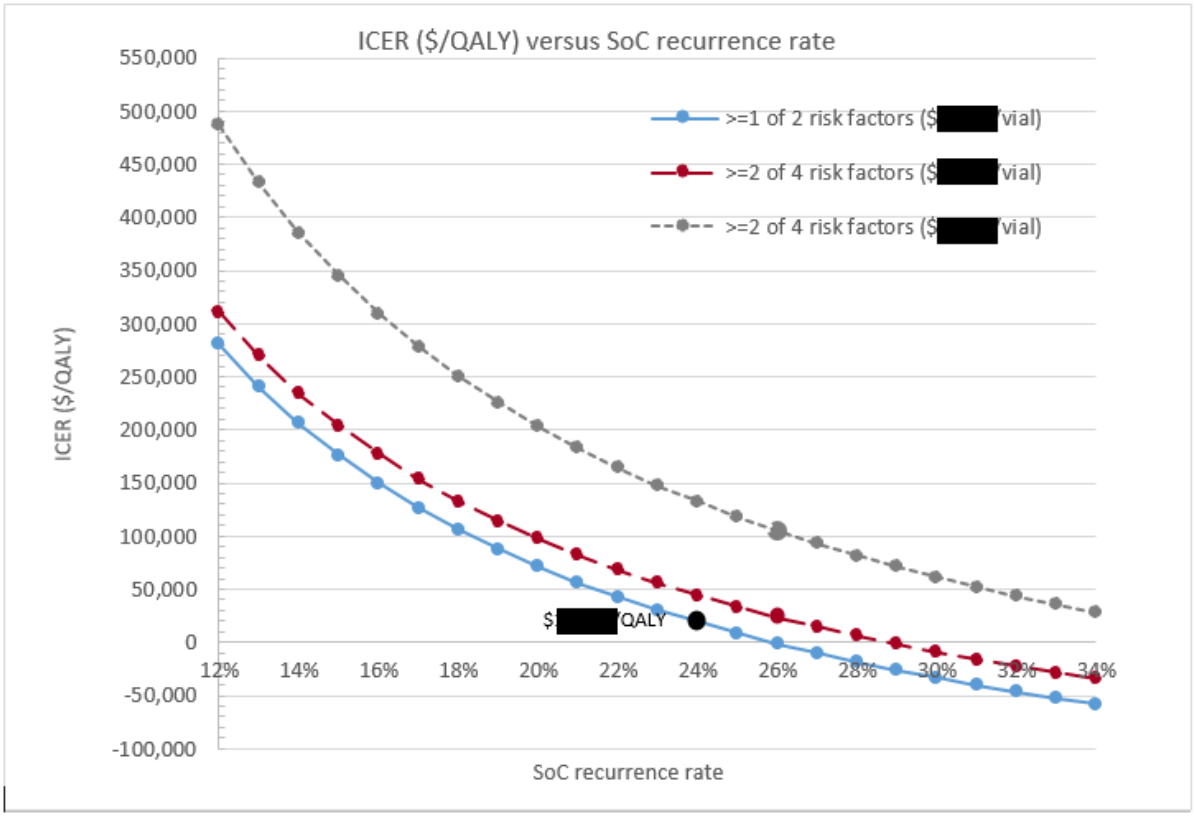
6.27 In July 2019, the ESC considered (as an example) that trial-based CDI recurrence rates by risk factor could be adjusted to reflect recurrence rates in the Australian population, using the aggregate recurrence rate cited by the Australian Commission on Safety and Quality in Health Care (ACSQHC) and the recurrence rates for the ITT population in the MODIFY trials. The adjustment resulted in CDI recurrence rates of 22% for patients with ≥1 of 4 and 26% for ≥2 of 4 risk factors. The PBAC however, considered that the CDI recurrence rate for SoC for the Australian population remained uncertain (paragraph 6.34, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

6.28 Based on the July 2019 ESC advice, the resubmission adjusted the trial-based CDI recurrence rate for SoC for patients with ≥1 of 2 risk factors from 32.3% to 23.9% in the model. The CDI recurrence rate for bezlotoxumab of 12.0% was then estimated by multiplying the adjusted baseline risk for SoC by the estimated treatment effect in the MODIFY trials. The treatment effect applied in the model did not take into account observed differences in baseline characteristics across the comparison groups for patients with ≥1 of 2 risk factors.

6.29 The resubmission and PSCR argued that the recurrence rates assumed in the model are conservative given results of a recent Australian study (Alfayyadh et al 2019). This retrospective cohort study examined CDI cases recorded in all public hospitals in Western Australia between October 2011 and July 2017, and found 31.9% (1471/4612) of patients experienced recurrent CDI. The ESC noted the CDI recurrence rates reported by Kerr et al 2019 for SoC with and without bezlotoxumab (9% and 33%, respectively) and those reported by Oski et al 2019 for patients treated with bezlotoxumab (27%) and considered that recurrence rates for the Australian population remain uncertain.

6.30 Figure 1 shows the relationship between CDI recurrence rate for SoC versus the ICER/QALY (at two different prices of bezlotoxumab) in the economic model for patients with ≥2 of 4 risk factors requested in the previous resubmission (July 2019) and ≥1 of 2 risk factors in this resubmission.

Figure 1: ICER modelled over varying 30-day first recurrence rate for SoC (assuming constant relative risk of 0.48 to estimate corresponding recurrence rate for bezlotoxumab)



Abbreviations: ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life years; SoC=standard of care
Source: constructed during the evaluation from Bezlotoxumab Section 3 Workbook of the resubmission

The figure shows an ICER between $15,000 to < $25,000/QALY.

6.31 The figure illustrates that the model remained highly sensitive to the CDI recurrence rate for SoC; and all else constant, that the lower requested price resulted in relatively larger decrease in the ICER than the updated population characteristics. The ICER was lower for patients with ≥1 of 2 risk factors than ≥2 of 4 risk factors due to the higher proportion of CDIs assumed to require hospitalisation (which favours bezlotoxumab) despite estimating slightly lower CDI recurrence for SoC and a slightly smaller treatment effect (which does not favour bezlotoxumab).

6.32 The figure also illustrates that the bezlotoxumab + SoC dominates SoC (i.e. larger benefit and lower cost) for CDI recurrence rates in the SoC arm above approximately 25.9%. Based on the CDI recurrence rates reported in the trials (32.3%) and Alfayyadh et al 2019 (31.9%), the ICERs were dominant.

6.33 Table 10 summarised the key drivers of the economic evaluation. Consistent with the previous submissions, the main drivers of the model remained CDI recurrence rates and other parameters that influence the extent of cost-offsets associated with hospitalisation (e.g. proportion hospitalised and proportion of recurrences which are severe) or drug costs. The actual proportion of hospitalisations in the Australian

population is unknown, using the lower end of the range in previous resubmissions (32% hospitalised instead of 56.7% used in the resubmission) increases the ICER to $75,000 to < $95,000/QALY.

Table 10: Key drivers of the model in the resubmission

Description	Method/Value	Impact Base case: $15,000 to < $25,000/QALY gained
CDI recurrence rate for SoC	The 30-day first CDI recurrence rate for SoC and bezlotoxumab were informed by results of (i) post-hoc subgroup analysis of the MODIFY trials (≥1 of 2 risk factors); and (ii) aggregate recurrence rate cited by the Australian Commission on Safety and Quality in Health Care (ACSQHC).	Very High The ICERs were dominant based on the trial-based rate and recent Australian data (Alfayyadh et al 2019).
Proportion of recurrences which are severe	Informed by results of post-hoc subgroup analysis of the MODIFY trials (≥1 of 2 risk factors). Salavert et al (2018) reported that this parameter varied widely across subgroups. Hence, the proportion of severe CDI recurrences in practice may depend on the number and type of risk factors present in the Australian population or may reflect random variation.	High, favours bezlotoxumab. The ICER increased to $25,000 to < $35,000/QALY assuming 12.9% after taking account of all CDI recurrences where patients can have more than one CDI recurrence.
Proportion of mild/moderate CDI requiring hospitalisation	Informed by post-hoc subgroup analysis of the MODIFY trials (≥1 of 2 risk factors). The ESC noted this parameter varied across subgroups and considered this may reflect true differences or random variation. The actual proportion of hospitalisations in Australia is unknown.	High, favours bezlotoxumab. The ICER increased to $55,000 to < $75,000/QALY assuming 40% based on the population requested in the previous resubmission.
Hazard ratio for CDI recurrence	Informed by results of post-hoc subgroup analysis of the MODIFY trials (≥1 of 2 risk factors). The ESC noted this parameter varied across subgroups and considered this may reflect true differences or random variation.	High, favours bezlotoxumab.
Hazard ratio for mortality with CDI recurrence versus no recurrence	Informed by lower 95% CI of the adjusted HR for mortality with CDI recurrence versus no recurrence estimated by Olsen et al 2015 (HR=1.33, 95%CI: 1.12, 1.59), as recommended by PBAC in July 2018.	High, favours bezlotoxumab, The ICER increased to $75,000 to < $95,000/QALY assuming no mortality benefit (i.e. HR = 1).

Shaded areas indicate data previously seen by the PBAC.
Source: Constructed during the evaluation.

6.34 Table 11 presents the results of the stepped economic evaluation for the population with ≥1 of 2 risk factors in this resubmission. The base case ICER was $$15,000 to < $25,000/QALY.

Table 11: Results of the stepped economic evaluation

Step and component	Bezlotoxumab + SoC	SoC only	Increment
Step 1: Used subpopulation with ≥1 of 2 risk factors from MODIFY I and MODIFY II			
Costs	$[redacted]	$0	$[redacted]
Outcomes (CDI recurrence rate)	11.96%	23.95%	11.99%
Cost per CDI recurrence avoided			$[redacted]
Step 2: Used Markov model to determine life years			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcomes (life years)	5.8613	5.8527	0.0086
Cost per life year gained			$[redacted]
Step 3: Applied utility weights to Markov model to determine QALYs			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	4.5402	4.5317	0.0085
Cost per QALY gained (base case)			**$[redacted]**
Step 3: Applied utility weights to Markov model to determine QALYs – July 2019 resubmission			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	4.3320	4.3202	0.0118
Cost per QALY gained (base case)			**$[redacted]**

Shaded areas indicate data previously seen by the PBAC.
Abbreviations: SoC=standard of care; QALY=quality adjusted life years
Source: Table 3-29, p159 and Bezlotoxumab Section 3 Workbook of the resubmission

6.35 In July 2019, the PBAC considered that the ICER was uncertain for several reasons including the requested population being poorly justified, the assumed CDI recurrence rates for SoC being unreliable, the magnitude of the treatment effect being inconsistent with the data from the MODIFY trials (difference of approximately -18% compared to -10% across the MODIFY ITT population) and the assumed mortality benefit not being supported by trial data. The PBAC also noted the lower effective price proposed in the pre-PBAC response (DPMQ of $[redacted]), however considered the resulting ICER ($15,000 to < $25,000/QALY) unreliable for the aforementioned reasons (paragraphs 6.44, 7.2, 7.6 and 7.9, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

6.36 The model remained sensitive to a number of parameters (see Table 10), but the ESC considered that the ICER presented in the current resubmission was probably more robust given the Sponsor attempted to address most of these concerns:

- The population in the model was restricted to patients ≥65 years of age or with a history of CDI in the past 6 months, consistent with the recommendations by the PBAC;
- The model assumed a more conservative estimate for CDI recurrence with SoC compared to the previous resubmission in July 2019 (23.9% vs 34.0%), and presented more reliable Australian data (Alfayyadh et al 2019) suggesting that the recurrence rate including relapse and re-infection is higher in practice than used in the resubmission.
- The model assumed a more conservative difference in the CDI recurrence rates for SoC and bezlotoxumab (approximately -12% vs -18%) as a result of assuming

a lower CDI recurrence rate for SoC, though the applied hazard ratio may not be conservative, i.e. it was lower than the hazard ratio for the full trial population and for other (larger) sub-groups.

- The resubmission noted that the model applied the mortality assumptions recommended by the PBAC in July 2018 and the model only estimated improved survival of approximately 3 days (discounted) for the treated cohort. The ICER however remained sensitive to the assumed small mortality benefit, increasing to $75,000 to < $95,000/QALY assuming no advantage.
- The Sponsor proposed a lower effective price of $[redacted] per bezlotoxumab vial compared to $[redacted] per vial in the previous pre-PBAC response and $[redacted] in the July 2019 resubmission.

6.37 The ESC considered that as patients immunocompromised due to a history of HSCT or SOT were not specifically included in the model the cost-effectiveness of bezlotoxumab in this population remains unknown. In addition, the ESC considered that the variation in the proportion of mild/moderate CDI cases requiring hospitalisation evident across submissions also remains a key area of uncertainty.

6.38 The PSCR (p2-3) updated the public/private split for use of bezlotoxumab, to ensure consistency across the economic analysis and financial implications of the resubmission. The split for the economic analysis was updated from 100% private use to 68:32 for public and private use, based on AIHW data of total hospital days across public and private hospitals (see paragraph 6.44). Using the updated split, the weighted price of bezlotoxumab (including administration fees and an additional specialist visit for a proportion of patients) reduced from $[redacted] to $[redacted] resulting in a reduction in the ICER from $15,000 to < $25,000/QALY to $15,000 to < $25,000/QALY.

6.39 Table 12 presents the results of key univariate sensitivity analyses. The ESC noted that the sensitivity analyses used the resubmission base case ICER of $15,000 to < $25,000/QALY.

Table 12: Results of key sensitivity analyses

Univariate analyses	Incremental costs	Incremental QALY	Cost per QALY
Changes in 30 day first CDI recurrence rate from index CDI episode			
- **Base case: Bezlotoxumab 12.0%, SoC 23.9%**	**$[redacted]**	**0.0085**	**$[redacted]**
- Assuming recurrence rate for SoC based on Western Australia data from Alfayyadh et al 2019: Bezlotoxumab 15.9% (assuming same relative risk reduction); SoC 31.9%	-$[redacted]	*0.0113*	Dominant
- Assuming recurrence rate for SoC based on data from MODIFY trial subgroup ≥1 of 2 risk factors: Bezlotoxumab 16.1%; SoC 32.3%	-$[redacted]	0.0114	Dominant*
Proportion of recurrences which are severe			
- **Base case: 15.0%**	**$[redacted]**	**0.0085**	**$[redacted]**
- 8.3% based on Salavert et al 2018	$[redacted]	0.0084	$[redacted]*
- 12.9% based on MODIFY subgroup taking account of all CDI recurrences where patients can have more than one CDI recurrence	$[redacted]	0.0085	$[redacted]*
Proportion of mild/moderate CDI requiring hospitalisation			
- **Base case: 56.7%**	**$[redacted]**	**0.0085**	**$[redacted]**
- 40% based on previous July 2019 resubmission	$[redacted]*	0.0085	$[redacted]*
- 32% based on previous July 2018 resubmission	$[redacted]*	0.0085	$[redacted]*
30 day mortality rate that were applied in the first 180 days in model			
- **Base case: 2.5% w/o recurrence and HR 1.12 with recurrence**	**$[redacted]**	**0.0085**	**$[redacted]**
- Using higher mortality rate for mortality without recurrence of 3.6% (Huber et al 2014)	$[redacted]*	0.0111*	$[redacted]
- Using mortality rate for mortality without recurrence of 7.3% (Chen et al 2017)	$[redacted]*	0.0183*	$[redacted]
- Using HR for mortality for recurrence of 1.33 (Olsen et al. 2015)	$[redacted]*	0.0199*	$[redacted]
- Using HR for mortality for recurrence of 1	$[redacted]*	0.0019*	$[redacted]*
RR of CDI recurrence for bezlotoxumab vs SOC**			
- **Base case: RR 0.50: Bezlotoxumab 12.0%, SOC 23.9%**	**$[redacted]**	**0.0085**	**$[redacted]**
- Assuming RR 0.56 (as per July 2018 model): Bezlotoxumab 13.5%, SOC 23.9%	$[redacted]	0.0074	$[redacted]
- Assuming RR 0.62 (as per trial ITT population): Bezlotoxumab 14.8%, SOC 23.9%	$[redacted]	0.0064	$[redacted]
Multivariate analysis**			
- Assuming RR 0.56: Bezlotoxumab 13.5%, SOC 23.9% AND - Assuming 12.9% of recurrences severe	$[redacted]	0.0074	$[redacted]
- Assuming RR 0.62%: Bezlotoxumab 14.8%, SOC 23.9% AND - Assuming 12.9% of recurrences severe	$[redacted]	0.0064	$[redacted]

Abbreviations: CDI=Clostridium difficile infection; SoC=standard of care (placebo); HR=hazard ratio; RR=relative risk.

* Indicates analyses conducted during the evaluation

** Indicates analyses conducted during the preparation of the ESC Advice

Source: Table 3-38, pp169-170 and Bezlotoxumab Section 3 Workbook of the resubmission

6.40 The PSCR (p2) noted the evaluation argument that the proportion of recurrences that may be severe proposed in the resubmission (15.7%) may be overestimated as the statistic does not take account of all CDI recurrences where patients can have more than one CDI recurrence. The PSCR (p2) acknowledged that the proportion of recurrences that may be severe reduced to 12.9% when the issue raised by the evaluation was taken into consideration. The ESC noted that this increased the ICER from $15,000 to < $25,000 to $25,000 to < $35,000 (Table 12).

6.41 The ESC considered it is not clear if there are differences in the relative treatment effect across sub-groups of patients with different risk factors, and noted that sensitivity analyses varying this parameter were not included in the submission or Commentary. These analyses have been added to Table 12, and the ESC noted that the ICER is sensitive to this parameter. The pre-PBAC response acknowledged the variation in treatment effect estimates across the submissions, noting that both the sponsor and the PBAC have had difficulty identifying the patient population that may benefit most from bezlotoxumab treatment. In adopting the patient population with risk factors of high prognostic value (and those with the history of transplant for which there is limited evidence), the sponsor considered that bezlotoxumab will be appropriately targeted. The pre-PBAC response argued that the relative treatment effect of 0.5 adopted in the economic model is a reasonable estimate to reflect the expected benefit of bezlotoxumab in the high-risk population requested in the resubmission. The pre-PBAC response noted that bezlotoxumab did not significantly reduce CDI recurrences versus placebo in patients with no risk factors (18.8% vs 20.9%, respectively; difference -2.1 [95% CI, -11.1, 6.9]).[4] As such, the pre-PBAC response argued it would be inappropriate to apply the treatment effect from the full trial population to a subgroup of patients who have at least one risk factor for which bezlotoxumab has been shown to significantly reduce CDI recurrences compared with placebo.

Drug cost/patient/course

6.42 The cost of bezlotoxumab per vial was $[redacted] (effective price, private use) and $[redacted] (effective price, public use). For the economic evaluation, the average cost per patient per course was $[redacted] assuming 4.4% of patients will require 2 vials and 100% private hospital use. For the financial estimates, the average cost per patient per course was $[redacted] assuming 4.4% of patients will require 2 vials and 50:50 private and public hospital use.

6.43 Table 13 compares drug costs between the trial, model and financial estimates.

[4] Gerding DN, Kelly CP, Rahav G, Lee C, Dubberke ER, Kumar PN, et al. Bezlotoxumab for prevention of recurrent Clostridium difficile infection in patients at increased risk for recurrence. Clin Infect Dis 2018; 67(5):649-656.

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

	Trials	Model	Financial estimates
Mean dose (mg)	730mg[a] administered	1044mg[b] costed	1044mg[b] costed
Mean duration	Single dose	Single dose	Single dose
Cost/patient	-	$[redacted]#	$[redacted]^
Cost/patient/course	-	$[redacted]#	$[redacted]^*

Private use

^ Assumed 50% public use and 50% private use

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

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

[b] 4.4% of patients assumed to weigh > 100 kg and require two vials of bezlotoxumab.

6.44 The PSCR updated the public/private hospital split for both the economic and financial estimates to 68% public use and 32% private use based on AIHW data of total hospital days across public and private hospitals. The revised cost/patient/course was $[redacted] for both the model and financial estimates.

Estimated PBS usage & financial implications

6.45 DUSC considered the first submission in November 2017; this resubmission was not considered by DUSC. The resubmission presented revised financial implications based on a new epidemiological approach to estimate the eligible population using hospital admission data, updated CDI recurrence rates in line with the economic evaluation and updated drug costs for treatment.

6.46 The PBAC had previously considered that the financial estimates were highly uncertain and likely an underestimate for several reasons including the derivation of the eligible population from oral vancomycin scripts on the PBS, which only accounted for approximately 10% of CDI related diarrhoeas (paragraphs 6.47 and 6.48; bezlotoxumab, Public Summary Document, July 2018 PBAC meeting).

6.47 The eligible PBS population estimated in the resubmission only included patients with ≥1 of 2 risk factors (i.e. age ≥65 years or history of CDI in the past 6 months) and did not include immunocompromised patients due to history of HSCT or SOT for whom listing was also requested. The Sponsor stated approximately 600 transplant patients will not meet the other eligibility criteria but the cost of treating those patients will be covered as part of the risk sharing arrangement.

6.48 Table 14 presents the key inputs for financial estimates.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Total CDI episodes	Total number of CDI episodes per year based on hospitalisations for CDI identified by diagnosis code A04.7 Gastroenterocolitis in 2015 and 2016	May be a potential underestimate (i) Use of hospitalisation data only may not capture patients with mild/moderate episodes of CDI currently treated in the community including nursing homes (i.e. without PBS listed bezlotoxumab available) but who may in the future be treated in hospital (with PBS – Section 100 listed bezlotoxumab available). The PSCR (p2) stated this was unlikely due to the need for an infusion. The ESC considered that treatment of CDI appears to be uncommon in Australian nursing homes (AC-NAPS 2015) but the overall prevalence of Australian community treatment of CDI was not known.
% in public hospitals	67.7% based on AIHW data (average 2014/15 to 2016/17)	
Population growth rate	1.6% per year based on ABS 2018 data.	(ii) The resubmission did not provide any justification for the assumption that all patients with a principal diagnosis of CDI are treated in public hospitals. The PSCR (p3) argued that patients who are admitted with a principal diagnosis of CDI are likely to be admitted following presentation to an Emergency Department (ED), with most EDs affiliated with public hospitals. The ESC noted that in 2017-18 public hospitals provided 92% of emergency admissions.[a]
% with positive toxin B	95% based on two Australian population-based studies (Roder et al 2015; Furuya-Kanomori et al 2017)	Unchanged from the previous resubmission but may be an overestimate as only 82% (106/129) tested positive for the toxin B gene in Roder et al 2015 and only half (49.7%, 773/1554) of the patients enrolled in the MODIFY trials had toxin B positive CDI.
% high risk (≥1 of 2 risk factors)	67.3% based on MODIFY subgroup data	Generally reasonable, given limited Australian data.
Uptake rate	40% in Year 1 increasing to 80% in Year 6. Based on assumptions.	Unchanged from the previous resubmissions.
Adjusting for CDI recurrence if bezlotoxumab is reimbursed	12% for bezlotoxumab and 23.9% for placebo, based on assumptions outlined in paragraph 6.28.	Methodology unchanged from the previous resubmission, but CDI recurrence rates were updated in line with the economic evaluation. It is not known what the true rate of recurrence is in the proposed population.
Bezlotoxumab dose/vials per patient	4.4%, based on proportion of patients weighing >100kg in the relevant MODIFY subgroup	Reasonable. Parameter revised from the previous resubmission based on the new subgroup.
MBS item	$99.50 for bezlotoxumab infusion based on MBS item 14245.	Item number unchanged from the previous resubmission but the unit cost was updated.

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

[a] Australian Institute of Health and Welfare 2019. Admitted patient care 2017–18: Australian hospital statistics. Health services series no. 90. Cat. no. HSE 225. Canberra: AIHW.

6.49 Table 15 presents the estimated use and financial implications of listing bezlotoxumab on the PBS.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of eligible patient episodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patient episodes treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of vials dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of bezlotoxumab						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for vancomycin						
Cost to PBS/RPBS less copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications (current resubmission)						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications (current resubmission – PSCR[b])						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous resubmission (July, 2019)						
Number of eligible patient episodes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patient episodes treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of vials dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Shaded areas indicate data previously seen by the PBAC

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

[a] Assuming 4.4% of patients use 2 bezlotoxumab vials.

[b] Public/Private hospital split updated from 50:50 to 68:32 and additional health care costs associated with infusion specific AEs or specialist visit costs included in updated financial estimates provided in the PSCR.

The redacted table shows that at Year 6, the estimated number of patients was 5,000 to < 10,000 and the vials dispensed was 5,000 to < 10,000; and the net cost to the PBS would be $10 million to < $20 million.

6.50 The total cost to the PBS/RPBS of listing bezlotoxumab was estimated to be $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing (a 19.5% reduction compared to the $60 million to < $70 million estimated over the first 6 years in July 2019). This reduction was driven by the [redacted]% reduction in the requested price per vial despite an increase in the number of patients treated.

6.51 The new epidemiological approach resulted in more treated patient episodes over the first 6 years than the previous approach. Compared to patients with >1 of 4 risk factors in the July 2018 resubmission, the new approach estimated a 6.2% increase for patients with >1 of 2 risk factors despite being a narrower population.

6.52 The PSCR updated the public/private split for use of bezlotoxumab, to ensure consistency across the economic analysis and financial implications of the

resubmission. The split in the financial estimates was updated from 50:50 to 68:32 for public and private use (see paragraph 6.44). The PSCR noted that this updated parameter had negligible impact on the financial estimates. The net cost to the PBS/RPBS was largely unchanged at $10 million to < $20 million in Year 6.

6.53 The PSCR also included additional health care costs associated with infusion specific AEs (specialist visit costs) in the financial estimates. As a result estimated cost to the MBS increased slightly from $0 to < $10 million to $0 to < $10 million in Year 6 (Table 15).

6.54 The PSCR advised that new and recurrent cases were included in the eligible population. The ESC noted that data on the effectiveness of recurrent dosing was not available. The ESC considered that if recurrent dosing was excluded from the restriction or 100% funded by the sponsor through the proposed risk sharing arrangement the financial estimates would need to be adjusted accordingly.

Financial Management – Risk Sharing Arrangements

6.55 The resubmission proposed a special pricing arrangement with effective DPMQ for bezlotoxumab of $[redacted] per vial (public hospitals) (versus a published price of $4,365).

6.56 The resubmission proposed a risk sharing arrangement with a cap/rebate structure to account for any uncertainty associated with the introduction of bezlotoxumab and the inclusion of transplant patients in the restriction. The cap structure was based on the financial estimates base case utilisation estimates presented in the resubmission up to Year 3, with the caps remaining at the Year 3 estimate of PBS costs of bezlotoxumab of $0 to < $10 million, for Year 3 to Year 6 (Table 16). The Sponsor proposed a rebate (undefined) for incremental payments over the cap. In the July 2019 resubmission, the Sponsor proposed a [redacted]% rebate for incremental payments over the cap.

Table 16: Risk sharing arrangement proposed for bezlotoxumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Subsidisation cap (current resubmission)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Subsidisation cap (current resubmission - PSCR)[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Constructed during the preparation of the ESC Advice from Bezlotoxumab Section 4 Workbook of the resubmission and PSCR
[a] Public/Private hospital split updated from 50:50 to 68:32 in the PSCR

6.57 The PBAC had advised that financial uncertainty would need to be addressed with a risk sharing arrangement with a [redacted]% rebate over the financial caps (paragraph 7.9, bezlotoxumab, Public Summary Document, July 2019 PBAC meeting).

6.58 The ESC noted that the PSCR did not clarify the proposed rebate for incremental payments over the cap. The ESC further noted detail regarding the inclusion of transplant patients in proposed risk sharing arrangements was not provided. The pre-PBAC response stated the sponsor agrees to the inclusion of transplant patients as per the prescriber instructions in the requested listing within the proposed RSA caps that

are capped at the Year 3 financial estimates in order to minimise the impact of uncertainty on Government expenditure. The pre-PBAC response also stated the sponsor agrees to a rebate for any incremental payment over the proposed RSA caps. The PBAC noted that the pre-PBAC response did not clarify the extent of the proposed rebate for incremental payments over the cap.

6.59 The ESC advised that in absence of any data on the effectiveness of recurrent dosing, cases where this occurs could be excluded from the restriction or [redacted]% funded by the sponsor through the proposed risk sharing arrangement. The ESC considered that the subsidisation caps would require amendment in accordance with adjustments to the financial estimates if these cases were removed (see paragraph 6.54). The pre-PBAC response stated that recurrent dosing in relation to the same episode of CDI has been addressed in the administrative advice section of the requested listing "Repeat administration is not permitted within 90 days of the initial episode". The pre-PBAC response argued that any incidence of CDI outside the 90 days is more likely to be a new case of CDI rather than a recurrence. In addition, the pre-PBAC response argued that, as the proposed RSA is based on utilisation estimates to Year 3 with expenditure in Years 4 to 6 capped at the Year 3 level, it has already been amended to account for any risk in repeat doses in the financial estimates.

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 uncertain clinical need, its modest effectiveness and concerns regarding safety, along with an uncertain incremental cost-effectiveness ratio (ICER).

7.2 The PBAC noted that the resubmission requested listing for a new high risk population, defined as ≥1 of 3 risk factors (age ≥65 years; history of CDI in past 6 months; immunocompromised due to haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)). The PBAC considered that restricting the population to age ≥65 years and history of CDI in past 6 months was consistent with the Committee's July 2019 advice. However, the PBAC noted the inclusion of an additional group of patients (immunocompromised due to HSCT or SOT) beyond that recommended in July 2019.

7.3 The PBAC noted the recent publication of the *Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice*.[5] The PBAC noted the consensus statements recommend antibiotics as first-

[5] Haifer C, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice Gut 2020;**0**:1–10. doi:10.1136/gutjnl-2019-320260

line therapy for an initial episode of CDI and faecal microbiota transplantation for patients with recurrent CDI. The PBAC considered that the 2020 Australian consensus statements confirm a shift in the clinical management algorithm for CDI with a preference for the use of faecal microbiota transplantation in the treatment of recurrence. The PBAC considered that antibiotics remain an appropriate alternative where faecal microbiota transplantation is not possible.

7.4 The comparator nominated by the resubmission was standard of care (SoC) antibacterial therapy including but not limited to vancomycin / metronidazole. The PBAC considered that, with the recent shift in the clinical management algorithm (see paragraph 7.3), the nominated comparator does not accurately reflect current clinical practice where faecal microbiota transplantation is a preferred treatment option in recurrent CDI.

7.5 The PBAC noted that the resubmission presented data for a post-hoc subgroup of patients with ≥ 1 of 2 risk factors (age ≥ 65 years and history of CDI in past 6 months) from the MODIFY trials. The PBAC reiterated its July 2019 advice that the Committee considered these risk factors were of high prognostic value. Despite adopting this risk stratification approach the PBAC considered that, although statistically significant, the clinical significance of a reduction in risk of CDI recurrence at 12 weeks of 15.6 percentage points (95% CI: -22.9, -8.3) was unclear.

7.6 The PBAC recalled that the MODIFY trials showed no evidence of a mortality benefit associated with bezlotoxumab compared to SoC. The PBAC also noted that faecal microbiota transplantation and subsequent lines of antibiotic therapy were available for the treatment of recurrent CDI. The PBAC reiterated its previous advice that the overall benefit of bezlotoxumab remained modest and was limited to a small difference in the prevention of CDI recurrence.

7.7 The PBAC noted the resubmission did not present any new safety data to support the claim of non-inferior safety, which was unchanged from the previous submissions. The PBAC recalled that, for the subset of patients in the MODIFY trials with a history of congestive heart failure (CHF) at baseline, the number of cardiac failure serious adverse events was higher in the bezlotoxumab arm than in the placebo arm (RD: 8% (95% CI 1%, 15%)). The PBAC reiterated its July 2019 advice that the claim of non-inferior comparative safety was not adequately supported by the data provided in the resubmission as the possibility of an increased risk of exacerbation of CHF for patients treated with bezlotoxumab in comparison to SoC remained.

7.8 The PBAC noted that the resubmission did not present any clinical trial data to inform the treatment effect or safety of bezlotoxumab for an immunocompromised population with HSCT or SOT. The PBAC agreed with the ESC that it was plausible for there to be differences in comparative effectiveness or safety outcomes for bezlotoxumab between the proposed immunocompromised population and the results reported in the MODIFY trials for patients with ≥1 of 2 risk factors (age ≥65 years, or history of CDI in the past 6 months). In addition, the PBAC noted that patients

immunocompromised due to a history of HSCT or SOT were not specifically included in the economic model and hence the cost-effectiveness in this population remains unknown.

7.9 The PBAC acknowledged the resubmission attempted to address previous concerns with the economic model as outlined in paragraph 6.36 and noted this included a lower effective price per bezlotoxumab vial ($[redacted] per vial versus $[redacted] in the July 2019 pre-PBAC response). The PBAC agreed with the ESC that the ICER presented in the current resubmission was probably more robust given the sponsors attempt to address previous concerns. However, the PBAC noted in the Pre-Sub-Committee Response (PSCR) the sponsor accepted the use of a lower estimate of the proportion of severe cases of CDI (12.9%) compared to that proposed in the base case (15.7%), which increased the ICER from $15,000 to < $25,000 to $25,000 to < $35,000. In addition, PBAC considered the ICER remained sensitive to the CDI recurrence rate and a number of other parameters including the assumed mortality benefit, the proportion of recurrences requiring hospitalisation, and the relative efficacy of bezlotoxumab in the proposed patient population. As such, the PBAC considered that the ICER remains uncertain and likely higher than proposed in the PSCR.

7.10 The PBAC noted the revised financial estimates presented in the resubmission.

7.11 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 through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Merck Sharp & Dohme disagrees with the PBAC's claim that there has been a recent shift in the clinical management of CDI, given that faecal microbiota transplantation is not yet established throughout Australia and there is a paucity of evidence in the specific populations that were the subject of this resubmission.

Merck Sharp & Dohme is disappointed that this fourth major submission was unsuccessful. This experience has reaffirmed our position that the ongoing Streamlined Pathways project is pivotal in ensuring that PBAC processes adapt to improve timely access for patients.