

MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
<p>BEZLOTOXUMAB</p> <p>Solution concentrate for I.V. infusion 1000 mg in 40 mL</p> <p>Zinplava®</p> <p>Merck Sharp &amp; Dohme (Australia) Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>Bezlotoxumab is indicated for the prevention of recurrence of <i>Clostridium difficile</i> infection (CDI) in adult patients 18 years or older at high risk for recurrence of CDI who are receiving antibiotic therapy for CDI</p>	<p>Bezlotoxumab is not currently PBS listed.</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority required listing for the treatment of patients at high risk of recurrence, defined as ≥1 of 3 risk factors (age ≥65 years; history of CDI in past 6 months; immunocompromised due to haematopoietic stem cell transplant or solid organ transplant).</p>	<p>The PBAC did not recommend the listing of bezlotoxumab on the PBS for the prevention of <i>Clostridium difficile</i> infection (CDI) on the basis of uncertain clinical need, its modest effectiveness and concerns regarding safety, along with an uncertain incremental cost-effectiveness ratio.</p>
			<p>Comparator: Standard of care (SoC)</p>	<p>The PBAC considered that due to a recent shift in the clinical management algorithm the nominated comparator does not accurately reflect current clinical practice where faecal microbiota transplantation is a preferred treatment option in recurrent CDI.</p>
			<p>Clinical claim: Superior comparative effectiveness and non-inferior comparative safety compared to SoC</p>	<p>The PBAC considered that the claim of superior comparative effectiveness was reasonable for patients with ≥1 of 2 risk factors (age ≥65 years or history of CDI in the past 6 months). However, the PBAC reiterated its previous advice that the overall benefit remained modest and the clinical relevance of the benefit unclear.</p> <p>The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.</p>
			<p>Economic claim: Cost-effectiveness basis compared to SoC</p>	<p>The PBAC acknowledged the resubmission attempted to address previous concerns with the economic model and noted this included a lower effective price per bezlotoxumab vial. However, PBAC considered the ICER remained sensitive to the CDI recurrence rate, 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 incremental cost-</p>

MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
				<p>effectiveness ratio remains uncertain and likely higher than proposed.</p>
<p>BROLUCIZUMAB</p> <p>Solution for intravitreal injection 19.8 mg in 0.165 mL pre-filled syringe</p> <p>Beovu®</p> <p>Novartis Pharmaceuticals Australia Pty Limited</p> <p>New listing (Minor Submission)</p>	<p>Brolucizumab is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).</p>	<p>Brolucizumab is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required listing for the treatment of patients with choroidal neovascularisation (CNV) due to AMD.</p> <p>Comparator: Aflibercept (main), ranibizumab (secondary)</p> <p>Clinical claim: Non-inferior effectiveness and safety compared to aflibercept</p>	<p>Sponsor's comment: Merck Sharp &amp; 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.</p> <p>Merck Sharp &amp; 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.</p> <p>The PBAC did not recommend brolucizumab for the treatment of patients with CNV due to AMD.</p> <p>While the PBAC considered that the claim of non-inferior efficacy was reasonable, it considered the claim of non-inferior safety remained uncertain. The PBAC considered the cost-minimisation analysis for this comparison was not adequately supported.</p> <p>The PBAC accepted that aflibercept and ranibizumab were appropriate comparators, consistent with the November 2019 PBAC meeting.</p> <p>The PBAC considered that the claim of non-inferior efficacy compared with aflibercept was reasonable, consistent with the November 2019 PBAC meeting. The PBAC considered the claim of non-inferior safety was not adequately supported due to the higher incidence of ocular serious adverse events reported for brolucizumab in clinical studies. The PBAC noted the American Society of Retinal</p>

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
				<p>Specialists had received anecdotal reports of retinal artery occlusion and intraocular inflammation following approval in the United States and considered this increased the uncertainty regarding comparative safety.</p> <p>Economic claim: Cost-minimisation versus ranibizumab</p> <p>The PBAC considered the cost-minimisation analysis was not adequately supported as the claim of non-inferior safety of brolocizumab was uncertain.</p> <p>Sponsor's comment: Novartis is disappointed with the PBAC outcome but will continue to work collaboratively with the PBAC, the Department of Health and Federal Government to ensure that Australians with age-related macular degeneration receive access to Beovu® through the Pharmaceutical Benefits Scheme at the earliest opportunity.</p>
<p><b>BUPRENORPHINE + NALOXONE</b></p> <p>Tablet (sublingual) containing 0.7 mg buprenorphine hydrochloride with 0.18 mg naloxone hydrochloride</p> <p>Tablet (sublingual) containing 1.4 mg buprenorphine hydrochloride and 0.36 mg naloxone hydrochloride</p> <p>Tablet (sublingual) containing 2.9 mg buprenorphine</p>	<p>Buprenorphine + naloxone is indicated for the treatment of opioid dependence, within a framework of medical, social and psychological treatment.</p>	<p>Buprenorphine + naloxone sublingual tablets is not currently PBS listed.</p>	<p>Resubmission to request a Section 100 (Opiate Dependence Treatment Program) Restricted Benefit listing for the treatment of patients with opiate dependence.</p> <p>Comparator: Suboxone®</p> <p>Clinical claim: Non-inferior safety and efficacy to Suboxone®</p>	<p>The PBAC did not recommend the listing of buprenorphine with naloxone sublingual tablets (Zubsolv®) for the treatment of patients with opioid dependence. The PBAC considered that no further evidence was provided in the resubmission to address the previous concerns raised regarding the uncertain equi-effective dose to buprenorphine with naloxone sublingual film (Suboxone®), unclear clinical need and significant quality use of medicines issues.</p> <p>The PBAC accepted that Suboxone® was an appropriate comparator, consistent with the November 2019 PBAC meeting.</p> <p>The PBAC noted the single arm extension study (OX219-008) that reported urine drug screen results up to 24 weeks, however considered that the updated data did not provide more certainty of non-inferiority beyond 15 days. Therefore, the PBAC maintained that the data presented</p>

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
hydrochloride and 0.71 mg naloxone hydrochloride Tablet (sublingual) containing 5.7 mg buprenorphine hydrochloride and 1.4 mg naloxone hydrochloride Tablet (sublingual) containing 8.6 mg and 2.1 mg naloxone hydrochloride Tablet (sublingual) containing 11.4 mg buprenorphine hydrochloride and 2.9 mg naloxone hydrochloride  Zubsolv®  Mundipharma Pty Ltd  New listing (Minor Submission)				did not adequately establish non-inferiority between Zubsolv® and Suboxone®.
			Economic claim: Cost-minimisation analysis compared to Suboxone®.	The PBAC noted the revised pricing structure proposed in the resubmission, but did not accept that this was sufficient to overcome the uncertainties in relation to dose equivalence between Zubsolv® and Suboxone® that was outlined in the November 2019 consideration.
			Sponsor's comment:	The sponsor had no comment.
CABOZANTINIB  Tablet 20 mg Tablet 40 mg Tablet 60 mg  Cabometyx®	Cabozantinib is indicated for the treatment of advanced renal cell carcinoma (RCC): <ul style="list-style-type: none"> <li>• in treatment-naive adults with</li> </ul>	Cabozantinib is currently PBS listed for the treatment of RCC in patients who have progressive disease following prior treatment with a	Resubmission to request an extension to the current Authority Required (STREAMLINED) listing for the treatment of Stage IV clear cell variant RCC to include patients who have not been previously treated with a TKI.	The PBAC did not recommend the listing of cabozantinib for the treatment of patients with stage IV clear cell variant RCC who have not previously been treated with a TKI. The PBAC considered that the comparative clinical benefit was small and uncertain, and the incremental cost-effectiveness ratio was significantly underestimated due to the inclusion of an overall survival benefit that was not supported by the clinical evidence. The PBAC considered that the overall

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
Ipsen Pty Ltd  Change to listing (Major Submission)	intermediate or poor risk  • in adults following prior treatment with vascular endothelial growth factor targeted therapy	tyrosine kinase inhibitor (TKI)		financial impact, including reductions in the use of cabozantinib in its existing later-line setting, were not reliably estimated in the resubmission.
			Comparator: Sunitinib	The PBAC considered that sunitinib and pazopanib are the appropriate main comparators, and that sunitinib was a reasonable proxy for pazopanib in terms of the clinical evidence presented.
			Clinical claim: Superior efficacy and different but broadly comparable safety compared with sunitinib	In the treatment-naïve setting, the PBAC considered that cabozantinib was associated with superior progression free survival but considered the magnitude was uncertain and likely overestimated given the small number of patients enrolled and the high potential risk of bias in the pivotal study, CABOSUN.  In the TKI-naïve post-immunotherapy setting, the PBAC considered that the claim of superior comparative effectiveness versus sunitinib was not adequately supported given the paucity of data that were specific to this setting, and the uncertain applicability of the CABOSUN trial to this setting. In both settings, the PBAC considered that the claim of different but broadly comparable safety compared with sunitinib was reasonable.
			Economic claim: Cost-utility analysis versus sunitinib	The PBAC considered that the resubmission had significantly underestimated the incremental cost-effectiveness ratio due to the inclusion of an overall survival benefit that was not supported by the clinical evidence, and post-progression costs that were inadequately supported.
			Sponsor's comment:	The sponsor had no comment.

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
<p>NABIXIMOLS</p> <p>Oromucosal spray, 8 mg per dose, 90 doses</p> <p>Sativex®</p> <p>Emerge Health Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>Nabiximols is indicated for symptom improvement in patients with moderate-to-severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.</p>	<p>Nabiximols is not currently listed on the PBS.</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing of nabiximols for the adjunctive treatment of moderate to severe spasticity in patients with MS who have not adequately responded to oral anti-spasticity agents.</p>	<p>The PBAC did not recommend the listing of nabiximols as an adjunctive treatment of moderate to severe spasticity due to MS.</p> <p>The key clinical trial (Markovà 2019) presented in the resubmission used an enriched population design in which non-responders to nabiximols were excluded from participation in the randomised phase of the study. The PBAC considered that, while the trial design was reasonable, it was likely to result in an overestimate of the clinical benefit and an underestimate of the adverse events for nabiximols.</p> <p>The PBAC considered the exclusion of non-responders also impacted on the generalisability of the trial results to the broader population of treated patients.</p>
			<p>Comparator: Standard care (current oral anti-spasticity medication)</p>	<p>The PBAC considered the nominated comparator was reasonable.</p>
			<p>Clinical claim: The submission claimed nabiximols, in combination with other oral anti-spasticity medication (standard care), was of superior effectiveness and inferior safety to standard care alone.</p>	<p>The PBAC considered the clinical claim of superior comparative effectiveness of nabiximols + standard care over standard care alone was reasonable, however considered the magnitude of benefit was uncertain and likely to be modest.</p> <p>The PBAC considered the clinical claim of inferior comparative safety to standard care alone was reasonable.</p>
			<p>Economic claim: cost-effectiveness and a cost-utility analysis compared to standard care alone.</p>	<p>The PBAC considered the economic model to be unreliable for decision making because:</p> <ul style="list-style-type: none"> <li>• The model structure was overly simplistic and did not capture the complexity of MS-related spasticity.</li> <li>• The clinical data that informs the model (Markova 2019) is likely to overestimate the clinical benefit and underestimate the adverse events for nabiximols.</li> </ul>

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
				<ul style="list-style-type: none"> <li>The cost offsets in the model were unrealistic and substantially overestimated as they assumed a majority of health system costs associated with management of MS would be avoided. The PBAC considered it was reasonable to assume only a portion of costs associated with the management of MS-related spasticity would be offset.</li> </ul> <p>The PBAC considered that while the economic model presented in the resubmission was unreliable, it was likely to have substantially underestimated the incremental cost-effectiveness ratio and considered a reasonable re-specified economic model would likely require the price of nabiximols to be reduced substantially to achieve a reasonable ratio.</p>
<p>PLITIDEPSIN</p> <p>Powder for IV infusion 2 mg with 4 mL solvent</p> <p>Aplidin®</p> <p>Specialised Therapeutics Pharma Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>Plitidepsin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior treatment regimens, including both a proteasome inhibitor (PI) and an immunomodulator (IMiD).</p>	<p>Plitidepsin is not currently PBS listed</p>	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority required listing for the treatment of patients with RRMM who are refractory to a PI and an IMiD (third-line) or in patients who have received at least three prior treatment regimens including both a PI and an IMiD (fourth-line).</p> <p>Comparator: Dexamethasone monotherapy (fourth-line) and pomalidomide with dexamethasone (third-line)</p> <p>Clinical claim: Superior effectiveness and inferior safety compared to</p>	<p>Sponsor's comment: Emerge Health looks forward to further constructive dialogues with the PBAC, to make this therapy available to patients on the PBS in the very near future.</p> <p>The PBAC did not recommend plitidepsin in combination with dexamethasone for the treatment of patients with RRMM. The PBAC considered non-inferiority versus pomalidomide was not demonstrated in the third-line setting. The PBAC considered cost-effectiveness of plitidepsin was not demonstrated in the fourth-line setting.</p> <p>The PBAC accepted that dexamethasone monotherapy (fourth-line) and pomalidomide with dexamethasone (third-line) were appropriate comparators, consistent with the July 2019 PBAC meeting.</p> <p>The PBAC considered the treatment comparison against dexamethasone monotherapy demonstrated only a marginal benefit in terms of progression free survival (PFS)</p>

**MARCH 2020 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
			<p>dexamethasone monotherapy (fourth-line). Non-inferior effectiveness and safety compared to pomalidomide with dexamethasone (third-line).</p>	<p>without progressive disease (PD) confirmation, and the clinical benefit attributed to PFS with PD confirmation was not reliable. The PBAC considered the overall survival gain was uncertain given it was statistically significant only when adjusted for cross-over. The PBAC agreed with the claim of inferior safety.</p> <p>The PBAC considered that, for the indirect comparison against pomalidomide with dexamethasone, the claim of non-inferior efficacy was uncertain, as a non-inferiority margin was not proposed, the point estimates of the hazard ratios from the indirect comparison favoured pomalidomide, and the 95% confidence intervals were wide. The PBAC considered the claim of non-inferior safety was not adequately supported.</p>
			<p>Economic claim: Cost-effectiveness versus dexamethasone monotherapy (fourth-line). Cost-minimisation versus pomalidomide with dexamethasone (third-line).</p>	<p>The PBAC considered there were significant issues with the base case of the economic model for the cost-utility analysis against dexamethasone monotherapy, leading to an underestimation of the incremental cost-effectiveness ratio in relation to: post-progression treatment costs, the PFS outcome used, and the source of utilities.</p> <p>The PBAC considered the clinical basis for the cost-minimisation analysis against pomalidomide with dexamethasone was not adequately supported.</p>
			<p align="center">Sponsor's comment:</p>	<p>The sponsor had no comment.</p>