

MARCH 2019 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>DARATUMUMAB</p> <p>Solution concentrate for IV infusion 100 mg in 5 mL, 400 mg in 20 mL</p> <p>Darzalex®</p> <p>Janssen-Cilag Pty Ltd</p> <p>New listing (Major submission)</p>	<p>DARATUMUMAB is indicated for use:</p> <ul style="list-style-type: none"> in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. 	<p>DARATUMUMAB is not currently PBS listed</p>	<p>Resubmission to request a Section 100 (Efficient funding for Chemotherapy) Authority Required listing:</p> <ul style="list-style-type: none"> in combination with bortezomib and dexamethasone (DBd) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have progressive disease after at least one prior therapy; and as monotherapy for highly treatment experienced or refractory patients with multiple myeloma. <p>Comparator:</p> <p>Combination therapy: bortezomib plus dexamethasone (Bd)</p> <p>Monotherapy: no comparator was nominated</p>	<p>The PBAC did not recommend the listing of daratumumab for use in combination with DBd in RRMM, on the basis of a high and uncertain cost-effectiveness ratio. The PBAC was also concerned about the very high estimated financial implications. The PBAC acknowledged the clinical need for additional treatments for RRMM and considered that daratumumab is an effective treatment; however, at the price proposed it was not a cost-effective treatment, even in the scenario proposed in the resubmission which included overly optimistic model assumptions regarding its benefits due to the use of a subgroup of the trial population, an uncertain adjustment for crossover and a benefit sustained over 15 to 20 years.</p> <p>The PBAC was unable to consider the listing of daratumumab monotherapy as a fourth-line treatment in highly treatment experienced or refractory patients with multiple myeloma as no comparative clinical or economic data were provided.</p> <p>The PBAC previously accepted Bd as the appropriate comparator for DBd.</p> <p>The PBAC noted that no comparator was nominated for daratumumab monotherapy. The PBAC noted that i) ESC had previously considered that pomalidomide would be a potentially relevant comparator (October 2017); and ii) a NICE technology appraisal guidance document in which that daratumumab monotherapy was indirectly compared with pomalidomide plus dexamethasone.</p>

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			<p>Clinical claim:</p> <p>Combination therapy: superior efficacy and inferior safety compared with Bd</p> <p>Monotherapy: no clinical claim was made</p>	<p>The PBAC again considered that the claims for combination therapy were reasonable.</p> <p>The PBAC considered that it was not possible to assess the comparative effectiveness or safety of monotherapy.</p>
			<p>Economic claim:</p> <p>Combination therapy: cost-effectiveness analysis compared with Bd</p> <p>Monotherapy: no cost-effectiveness analysis was presented</p>	<p>The PBAC identified two key issues with the economic analysis for combination therapy: that the time horizon of 20 years (reduced to 15 years in the pre-PBAC response) remained too long, with the PBAC again advising that a 10 year time horizon would be appropriate; and that the base case analysis used a subgroup in which efficacy was improved to inform the model, rather than the total trial population. The PBAC considered that the resulting cost effectiveness analysis was favourable to DBd treatment. The PBAC considered that at the proposed price, DBd was not cost-effective.</p> <p>The PBAC was unable to assess the cost-effectiveness of monotherapy.</p>
			<p>Sponsor's comments:</p>	<p>The sponsor had no comment.</p>
<p>DARBEPOETIN ALFA</p> <p>Injection 200 micrograms in 0.4 mL pre-filled syringe Injection 300 micrograms in 0.6 mL pre-filled syringe</p>	<p>DARBEPOETIN ALFA is indicated for:</p> <ul style="list-style-type: none"> the treatment of anaemia associated with chronic renal failure (CRF). the treatment of 	<p>DARBEPOETIN ALFA is currently PBS listed for anaemia associated with intrinsic renal failure</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drugs) Authority Required listing for chemotherapy-induced anaemia.</p>	<p>The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing of darbepoetin alfa for the treatment of moderate to severe chemotherapy-induced anaemia. This decision was due to an uncertain clinical need and ongoing concerns regarding overall mortality and venous thromboembolism rates with darbepoetin alfa across the proposed PBS population.</p>

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<p>Injection 500 micrograms in 1 mL pre-filled syringe</p> <p>Aranesp®</p> <p>Amgen Australia Pty Ltd</p> <p>Change of listing (Major Submission)</p>	<p>anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy.</p>		<p>Comparator: standard medical management</p>	<p>The PBAC considered that the comparator of standard medical management was appropriate.</p>
			<p>Clinical claim: superior efficacy and non-inferior safety compared with standard medical management</p>	<p>The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data for haemoglobin and transfusion outcomes. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.</p>
			<p>Economic claim: cost-effectiveness analysis compared with standard medical management.</p>	<p>The PBAC considered that the selective use of data from Study 231 in the economic model meant that the proportion of patients who received a red blood cell transfusion in the standard medical management arm was overestimated. In addition, the PBAC considered the cost of transfusion used in the model was unreasonably high. Overall the PBAC considered that the cost effectiveness of darbepoetin alfa for chemotherapy induced anaemia was highly uncertain.</p>
			<p>Sponsor's comments:</p>	<p>The sponsor had no comment.</p>
<p>ERENUMAB</p> <p>Injection 70 mg in 1 mL single dose pre-filled pen</p> <p>Aimovig®</p> <p>Novartis Pharmaceuticals Australia Pty Ltd</p> <p>New listing</p>	<p>ERENUMAB is indicated for prophylaxis of migraine in adults.</p>	<p>ERENUMAB is not currently PBS listed</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for prophylaxis in patients with chronic migraine.</p>	<p>The PBAC did not recommend the Authority Required (STREAMLINED) listing of erenumab for the treatment of patients with chronic migraine. The PBAC considered the magnitude of the clinical benefit, and the claim of non-inferior efficacy compared with Botox, were uncertain due to being based on a subgroup of the trial population and clinical data for only the 140 mg dose.</p> <p>There were significant issues with the economic model, and the cost-effectiveness of erenumab versus BSC at the price proposed in the resubmission is highly uncertain. The expected financial impact of listing erenumab on the PBS was very high and uncertain. Given</p>

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(Major Submission)				the significant burden of disease and the high number of patients that may benefit from treatment, the PBAC considered it was important to ensure any PBS listing was based on the best available data, was appropriately targeted to the right patients and was cost-effective in those patients.
			Comparator: Botulinum toxin type A (Botox®) and Best Supportive Care (BSC)	Accepted. The PBAC did not consider the weighting across the comparators to be adequately supported. Further, the PBAC did not consider the differential price for the two groups of patients (those treated with Botox versus those not treated with Botox) to be adequately justified.
			Clinical claim: Superior comparative efficacy and safety versus BSC Non-inferior comparative efficacy and safety versus Botox.	Not accepted. The PBAC noted the clinical claims in the resubmission were based on a small subgroup of patients in the pivotal study and considered the use of a subgroup to support the comparisons to BSC and Botox was inadequately supported. The PBAC noted erenumab decreased monthly migraine days (MMD) and achieved a higher proportion of patients with a 50% reduction in MMD over 12 weeks of treatment compared with BSC but considered the magnitude and clinical significance of the benefit was uncertain. The uncertainty was increased by the lack of data provided for the 70 mg dose. The PBAC considered there were significant transitivity issues with the indirect comparison to Botox as there were substantial differences in responses observed in the placebo arms of the two studies being indirectly compared.

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			<p>Economic claim: Cost-effectiveness versus BSC Cost-minimisation versus Botox</p>	<p>Not Accepted.</p> <p>The PBAC considered there were significant issues with the economic model and, in addition to the uncertainty of the clinical benefit in the subgroup population, considered it was of limited value in determining the cost-effectiveness of erenumab.</p> <p>The PBAC considered a cost-minimisation analysis may not be appropriate as non-inferiority was not supported with the data presented in the resubmission.</p>
			<p>Sponsor's comments:</p>	<p>Novartis is disappointed for the migraine community with the committee's decision not to recommend the reimbursement of erenumab. Nevertheless, the clinical need for a new therapy in migraine is evident through the broad range of consumer comments and the PBAC noting that there is a significant burden of disease and a high number of patients that may benefit from treatment. Novartis remains committed to exploring options with the PBAC and The Department to enable access to erenumab for Australian migraine patients.</p>
<p>INSULIN GLARGINE with LIXISENATIDE</p> <p>Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 50 micrograms per mL, 3 mL, 5</p>	<p>INSULIN GLARGINE with LIXISENATIDE is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by</p>	<p>INSULIN GLARGINE with LIXISENATIDE is not currently PBS listed</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for the treatment of patients with T2DM who have inadequate glycaemic control with basal insulin.</p> <p>Comparator: Exenatide twice daily plus insulin glargine.</p>	<p>The PBAC did not recommend the listing of insulin glargine with lixisenatide fixed ratio combination (FRC) for treatment of adults with T2DM who have inadequate glycaemic control with basal insulin on the basis that the proposed price was unacceptably high given the residual uncertainty around the claim of non-inferiority and the appropriate equi-effective doses.</p> <p>The PBAC considered that the comparator proposed by the submission remained appropriate.</p>

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Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 33 micrograms per mL, 3 mL, 5 Soliqua® Sanofi-Aventis Australia Pty Ltd New listing (Major Submission)	metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin		Clinical claim: Non-inferior efficacy and safety	The PBAC reiterated its March 2018 advice that the claim of non-inferior comparative effectiveness was uncertain but may be reasonable.
			Economic claim: Cost-minimisation based on an assumed 1:1 dose relativity of lixisenatide and exenatide.	The PBAC considered the revised equi-effective ratio may remain optimistic, as the PBAC had previously considered lixisenatide may be inferior to exenatide on a microgram to microgram basis.
			Sponsor's comments:	Sanofi is disappointed by the Committee's decision. The fixed ratio combination of lixisenatide with insulin glargine provides a convenient alternative treatment option for Australian diabetics and we will continue to work towards providing access to this medicine.
LETERMOVIR Tablet 240 mg Prevymis® Merck Sharp and Dohme (Australia) Pty Ltd New listing (Major Submission)	LETERMOVIR is indicated for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT)	LETERMOVIR is not currently PBS listed	Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the prophylaxis of CMV infection or disease in adult CMV-seropositive recipients of allogeneic HSCT.	The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing for letermovir for prophylaxis of CMV infection or disease in CMV seropositive patients who have received an allogeneic HSCT.
			Comparator: placebo	The PBAC advised that, in addition to placebo, a comparison of letermovir with antivirals as prophylaxis for CMV was required to inform decision making.

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			Clinical claim: superior comparative efficacy and non-inferior comparative safety	The PBAC considered that the claim of superior comparative effectiveness compared with pre-emptive therapy or other antivirals used as prophylaxis was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative safety was reasonably supported by the data.
			Economic claim: cost-effectiveness analysis against placebo	The PBAC acknowledged the clinical utility of letermovir for this indication but considered that the mortality and re-hospitalisation benefits attributed to letermovir were not supported by the trial evidence provided in the resubmission. As these outcomes formed the basis of the revised economic model the PBAC considered that the cost-effectiveness of letermovir was unable to be assessed.
			Sponsor comments:	The sponsor is disappointed that the PBAC has not recognised the benefits that letermovir would bring to patients undergoing allogeneic bone marrow transplants who are at risk of CMV reactivation. MSD will continue working to gain access for Australian patients.
<p>NIVOLUMAB</p> <p>Injection concentrate for IV infusion 40 mg in 4 mL, 100 mg in 10 mL</p> <p>Opdivo®</p> <p>Bristol-Myers Squibb Australia Pty Ltd</p> <p>Change to listing</p>	<p>NIVOLUMAB, as monotherapy, is indicated for:</p> <ul style="list-style-type: none"> Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. 	<p>NIVOLUMAB, as monotherapy, is currently PBS listed for:</p> <ul style="list-style-type: none"> Unresectable Stage III or Stage IV malignant melanoma Locally advanced or metastatic non-small cell lung 	<p>Resubmission to request an extension of the current Section 100 – Efficient Funding of Chemotherapy Authority Required (STREAMLINED) listing of nivolumab to include adjuvant treatment for completely resected Stage III or completely resected Stage IV melanoma.</p>	<p>The PBAC decided not to recommend nivolumab as an adjuvant treatment for completely resected Stage III or IV melanoma. The PBAC again acknowledged that there was a high unmet clinical need for effective therapies to reduce the risks of recurrence, and considered that in some circumstances recurrence was less likely for nivolumab compared with placebo. However, the PBAC remained concerned that there was uncertainty in the magnitude of the clinical benefit and in the incremental cost-effectiveness ratio (ICER) due to the immaturity of the data, and that the estimated financial impact remained high and uncertain.</p>

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(Major submission)	<ul style="list-style-type: none"> • Patients with unresectable or metastatic melanoma • Locally advanced or metastatic squamous non-small cell lung cancer with progression on or after prior chemotherapy • Locally advanced or metastatic non-squamous non-small cell lung cancer with progression on or after prior chemotherapy • Advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy • Relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab 	<p>cancer</p> <ul style="list-style-type: none"> • Stage IV clear cell variant renal cell carcinoma • Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx 		The PBAC considered the PBS listing should be for resected Stage IIIB, Stage IIIC, Stage IIID and Stage IV melanoma.
			Comparator: observation as standard of care was the main comparator	The PBAC had previously accepted that the comparator was reasonable.
			Clinical claim: superior in terms of effectiveness and 'moderately' inferior in terms of safety compared with placebo	<p>The PBAC considered that nivolumab was superior in terms of comparative effectiveness in patients with Stage IIIB, IIIC, IIID and Stage IV completely resected melanoma compared with placebo.</p> <p>The PBAC considered that nivolumab was inferior to placebo in terms of comparative safety.</p>
			Economic claim: cost-effectiveness analysis presented	The PBAC considered that the resultant ICER was high and also uncertain as there was a lack of data supporting the modelled continued treatment effect and the impact of treatment on overall survival. In addition, the overall survival in the observation arm was considered pessimistic when compared with other published models. The PBAC considered that a price reduction would be required for nivolumab to be considered cost effective in the adjuvant setting.
			Sponsor's comments:	The sponsor had no comment.

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	<p>vedotin</p> <ul style="list-style-type: none"> • Recurrent or metastatic squamous cell cancer of the head and neck in patients progressing on or after platinum based therapy • Locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy • Hepatocellular carcinoma after prior sorafenib therapy <p>NIVOLUMAB, in combination with ipilimumab, is indicated for:</p> <ul style="list-style-type: none"> • Unresectable or metastatic melanoma • Intermediate/poor-risk, previously untreated renal cell 			

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	carcinoma			
<p>PERTUZUMAB</p> <p>Solution for I.V. infusion 420 mg in 14 mL</p> <p>Perjeta®</p> <p>Roche Products Pty Ltd</p> <p>Change to listing (Major Submission)</p>	<p>PERTUZUMAB is indicated for:</p> <ul style="list-style-type: none"> • Early Breast Cancer: Perjeta is indicated in combination with trastuzumab and chemotherapy for: the neoadjuvant treatment of patients with human epidermal growth factor receptor-2 positive (HER2+) inflammatory; or locally advanced, or early stage (either > 2 cm in diameter or node positive) breast cancer as part of a complete 	<p>PERTUZUMAB is currently PBS listed for:</p> <ul style="list-style-type: none"> • Metastatic (Stage IV) HER2+ breast cancer • HER2+breast cancer 	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing in combination with trastuzumab and chemotherapy, for the adjuvant treatment of HER2+ lymph node positive early breast cancer (eBC).</p> <p>Comparator: trastuzumab in combination with chemotherapy (T+Chemo)</p>	<p>The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy), Authority Required listing of pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of HER2+, lymph node positive, eBC.</p> <p>The PBAC considered that the clinical place for pertuzumab in the adjuvant setting is unclear given the shift towards treating high-risk patients in the neoadjuvant setting and the lack of data for adjuvant pertuzumab following neoadjuvant treatment. The PBAC's concerns remained regarding the small benefit with the addition of pertuzumab in terms of invasive disease free survival (with overall survival data pending), balanced against the increased risk of adverse events and the impact of additional treatment infusions on both patients and the health care system.</p> <p>The PBAC previously accepted that the comparator was T+Chemo.</p>

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	<p>treatment regimen for early breast cancer; the adjuvant treatment of patients with HER2+ early breast cancer at high risk of recurrence.</p> <ul style="list-style-type: none"> Metastatic Breast Cancer: Perjeta is indicated in combination with trastuzumab and docetaxel for patients with metastatic HER2+ breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease. 		<p>Clinical claim: superior comparative effectiveness and inferior comparative safety compared with T+Chemo.</p> <p>Economic claim: cost-utility basis compared with T+Chemo</p> <p>Sponsor's comments:</p>	<p>The PBAC maintained its view that the claim of superior comparative effectiveness was reasonable in terms of the risk of recurrence but the magnitude of benefit was small.</p> <p>The claim of inferior safety was reasonable and was supported by the data.</p> <p>The PBAC maintained its view that despite the additional information presented in the resubmission, the same uncertainties remain as the benefit to harm ratio was essentially unchanged from the previous submission.</p> <p>The PBAC considered that the incremental cost-effectiveness ratio (ICER) for pertuzumab remained uncertain because much of the assumed benefit in the model relied on extrapolation of outcomes and external data sources.</p> <p>The PBAC considered that the ICER for pertuzumab remained uncertain because much of the assumed benefit in the model relied on extrapolation of outcomes and external data sources, and the base case ICER was dependent on a reduction in the cost of trastuzumab. The PBAC's concerns regarding the sponsor's price proposal were secondary to its concerns about the extent of clinical benefit with pertuzumab and its clinical place in eBC therapy.</p> <p>The sponsor had no comment.</p>

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<p>SODIUM PHENYLBUTYRATE</p> <p>Granules 483 mg (as sodium) per g, 174 g</p> <p>Pheburane®</p> <p>Orpharma Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>SODIUM PHENYLBUTYRATE is indicated for the management of hyperammonaemia associated with urea cycle disorders (UCD).</p>	<p>SODIUM PHENYLBUTYRATE is not currently PBS listed</p>	<p>Resubmission to request an Authority Required listing for a sugar-coated granule formulation of sodium phenylbutyrate (referred to as 'coated NaPb') for the treatment of patients with UCD.</p>	<p>The PBAC did not recommend the listing of a sugar-coated granule formulation of sodium phenylbutyrate (referred to as 'coated NaPb') on the basis that the proposed clinical place, which was as a second-line therapy after failure and/or intolerance to a medicine that is neither TGA-registered nor PBS-listed (sodium benzoate, NaBz), was inappropriate, and the cost-minimisation analysis had significantly overestimated the cost of the comparator.</p> <p>The PBAC reiterated its previous consideration that ammonia scavengers have an important clinical place, and that there is a need to ensure the continuing availability of NaPb. The PBAC considered that, given there is currently no TGA-approved or PBS-listed product in Australia for this condition, it would be beneficial to list coated NaPb if the above issues were able to be addressed.</p>
			<p>Comparator: The comparator nominated by the resubmission was uncoated NaPb powder compounded into an oral suspension or capsules by a compounding pharmacy.</p>	<p>The PBAC reiterated its November 2017 and March 2018 consideration that NaBz was also a relevant comparator.</p>
			<p>Clinical claim: coated NaPb is non-inferior in terms of effectiveness and safety compared with uncoated NaPb (for patients who were intolerant to or inadequately controlled by NaBz or requiring combination therapy).</p>	<p>The PBAC considered that the claim of non-inferior comparative effectiveness to uncoated NaPb was reasonable when the line of therapy was not specified.</p> <p>The PBAC reiterated its previous consideration that coated NaPb was non-inferior in terms of comparative efficacy and safety compared with other ammonia scavengers (uncoated NaPb and NaBz).</p>

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			<p>Economic claim: cost-minimisation analysis versus compounded NaPb, i.e. uncoated NaPb powder that was compounded into an oral suspension or capsules by a compounding pharmacy.</p>	<p>The PBAC considered that the resubmission's cost-minimisation analysis had significantly overestimated the cost of the comparator because the analysis: included significant costs for compounding, wastage, mark-ups or other fees that accounted for approximately 80% of the proposed costs; and did not include the cost-offset for compounding the coated tablets into a liquid solution for patients with nasogastric or gastrostomy tubes. Overall, the PBAC considered that the cost-minimisation analysis did not reflect the cost of compounded ammonia scavengers that would be applicable under the PBS.</p>
			<p>Sponsor's comment:</p>	<p>Orpharma will continue to work with the PBAC and will address the ongoing concerns raised in order to make Pheburane available.</p>