

JULY 2016 PBAC OUTCOMES – 1ST TIME DECISIONS NOT TO RECOMMEND

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRUG TYPE AND USE	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
BRIVARACETAM 25 mg tablet, 56 50 mg tablet, 56 75 mg tablet, 56 100 mg tablet, 56 10 mg/mL, 300 mL Briviact® UCB Australia Pty Ltd New listing (Major Submission)	Epilepsy	Authority Required (STREAMLINED) listing for treatment of partial epileptic seizures.	The PBAC did not recommend the listing of brivaracetam for intractable partial epileptic seizures on the basis of a lack of clinical data for use in the requested PBS population, and lack of a comparison with levetiracetam, or other similarly listed anti-epileptic drugs, which the PBAC considered would be replaced by brivaracetam. The PBAC noted the submission considered that brivaracetam should be used before lacosamide and considered this was inconsistent with selecting lacosamide as the comparator.
		Sponsor comment:	UCB is disappointed regarding the PBAC outcome, however UCB will continue to work with the Department and the PBAC to secure reimbursement of Briviact for patient benefit.

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<p>DACTYLIS GLOMERATA with POA PRATENSIS, LOLIUM PERENNE, ANTHOXANTHUM ODORATUM and PHLEUM PRATENSE</p> <p>100 IR tablet: sublingual, 3 + 300 IR tablet: sublingual, 28; 300 IR tablet: sublingual, 30</p> <p>Oralair[®]</p> <p>Stallergenes Australia Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	<p>Allergic rhinitis due to grass pollens</p>	<p>Authority Required (STREAMLINED) listing for allergic rhinitis due to grass pollen.</p>	<p>The PBAC did not recommend the listing of a sublingual form of allergen immunotherapy, Dactylis glomerata with Poa pratensis with Lolium perenne with Anthoxanthum odoratum and Phleum pratense (referred to by the trade name, Oralair[®]), on the PBS for allergic rhinitis due to grass pollen. In reaching this conclusion, the PBAC considered that the magnitude of clinical benefit was unclear and the cost-effectiveness of the requested listing was unknown.</p> <p>On the basis of the meta-analysed results of the clinical trials presented in the submission, Oralair compared with placebo resulted in:</p> <ul style="list-style-type: none"> • A reduction in symptoms as measured by the average rhinoconjunctivitis total symptom score (ARcTSS) score, of 1.0 on the 18-point symptom scale. A one point reduction in the symptom score represents a reduction in the severity of one of six allergic rhinitis symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) from severe to moderate, moderate to mild, or mild to no symptom. The PBAC noted that the six allergic rhinitis symptoms may not be all equally relevant in patients suffering from allergic rhinitis due to grass pollen. • A 6% increase in the number of days in which allergic rhinitis symptoms were controlled without the use of symptomatic treatments (e.g. oral antihistamines, nasal corticosteroids). With an average duration of pollen season of approximately 2 months across the trials, this translates to an additional 3.5 symptom controlled days. <p>The PBAC considered the clinical evidence presented in the submission to be difficult to interpret and therefore considered the likely treatment benefits to be uncertain.</p> <p>The PBAC considered the cost effectiveness was hard to interpret as the submission effectively modelled outcomes in terms of rhinitis symptom adjusted life years (RSALYs) instead of quality adjusted life years (QALYs) and therefore the results did not allow for a comparison of cost effectiveness to other health interventions. In addition, the incremental cost effectiveness per RSALY was uncertain as the model did not adequately account for the substantial variability expected in treatment effects due to variations of patient characteristics and allergen exposure (including length of pollen season). Further,</p>

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			The PBAC considered that the estimated financial implications and utilisation were uncertain and likely to be underestimated.
		Sponsor comment:	Stallergenes is committed to working with the PBAC and the Department of Health to provide access to this therapeutic alternative for patients with moderate to severe allergic rhinitis induced by grass pollen who are not properly controlled by standard treatments.

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<p>HOUSE DUST MITE AMERICAN with HOUSE DUST MITE EUROPEAN</p> <p>100 IR tablet: sublingual, 3 + 300 IR tablet: sublingual, 28; 300 IR tablet: sublingual, 30</p> <p>Actair[®]</p> <p>Stallergenes Australia Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	<p>Allergic rhinitis due to house dust mites</p>	<p>Authority Required (STREAMLINED) listing for allergic rhinitis due to house dust mite.</p>	<p>The PBAC did not recommend the listing of a sublingual form of allergen immunotherapy, house dust mite American with house dust mite European (referred to by the trade name Actair[®]) on the PBS for allergic rhinitis due to house dust mites. In reaching this conclusion, the PBAC considered that the magnitude of clinical benefit was unclear, and the estimate of cost-effectiveness as presented in the submission was unknown.</p> <p>On the basis of the evidence presented in the submission for Actair compared to placebo resulted in an average reduction in symptoms, as measured by the rhinitis total symptom score of between 0.62 (on a scale of 0 to 12) as measured in trial VO57.07, to 1.31 (on a scale of 0 to 15) in trial 1207d1731. A 1 point reduction in symptom scores represents a reduction in the severity of one of four symptoms (sneezing, rhinorrhoea, nasal congestion, nasal pruritus) from severe to moderate, moderate to mild, or mild to no symptoms.</p> <p>The PBAC considered the clinical evidence presented in the submission to be difficult to interpret and therefore considered the likely benefits to patients to be uncertain.</p> <p>The PBAC considered the cost effectiveness was hard to interpret as the submission effectively modelled outcomes in terms of rhinitis symptom adjusted life years (RSALYs) instead of quality adjusted life years (QALYs) and therefore the results did not allow for a comparison of cost effectiveness to other health interventions. In addition, the incremental cost effectiveness per RSALY was uncertain as the model did not adequately account for the substantial variability expected in treatment effects due to variations of patient characteristics and allergen exposure. Further, the submission assumed a sustained and constant treatment effect of six years after three years of treatment which the PBAC considered was not adequately supported by the clinical evidence.</p> <p>The PBAC considered that the estimated financial implications 4 and utilisation were uncertain and likely to be underestimated.</p>

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		Sponsor comment:	Stallergenes is committed to working with the PBAC and the Department of Health to provide access to this therapeutic alternative for patients with moderate to severe allergic rhinitis due to House Dust Mites who are not properly controlled by standard treatments.

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<p>LENALIDOMIDE</p> <p>5 mg capsule, 21 10 mg capsule, 21 15 mg capsule, 21 25 mg capsule, 21</p> <p>Revlemid®</p> <p>Celgene Pty Ltd</p> <p>Change to listing (Major Submission)</p>	<p>Relapsed or refractory mantle cell lymphoma</p>	<p>Authority Required listing for treatment of relapsed or refractory mantle cell lymphoma.</p>	<p>The PBAC decided not to recommend the listing of lenalidomide for relapsed/refractory mantle cell lymphoma, on the basis of uncertain effectiveness, with no overall survival gain demonstrated in the trial, and uncertain cost-effectiveness. The PBAC were of the view that many assumptions used in the estimation of the cost-effectiveness were optimistic, and that the incremental cost-effectiveness ratio (ICER) was therefore likely to be higher than estimated in the submission.</p> <p>In making this decision, the PBAC recognised that there is a need for a treatment option that induces a high response rate with minimal toxicity for patients with relapsed/refractory mantle cell lymphoma, who are unsuitable for chemotherapy. The extent to which the addition of lenalidomide would improve management in this population of patients with poor prognosis remained unknown.</p> <p>On the basis of direct evidence presented by the submission, in comparison with investigator's choice of chemotherapy, lenalidomide monotherapy resulted in:</p> <ul style="list-style-type: none"> • A reduction of approximately 39% in the risk of a disease progression event over a duration of follow-up of 15.9 months; and • No statistically significant improvement in overall survival over a duration of follow-up of 15.9 months. <p>For every 100 patients treated with lenalidomide in comparison with investigator's choice over a median duration of follow-up of approximately 15.9 months:</p> <ul style="list-style-type: none"> • 5 more patients will experience Grade 3 or 4 nervous system disorders; and • 4 more patients will experience Grade 3 or 4 pulmonary embolism.

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		Sponsor comment:	Celgene acknowledges some of the limitations in the data but will work constructively with the PBAC to try and mitigate some of the outstanding issues as there is a clear need for effective options for these patients.
<p>NIVOLUMAB</p> <p>40 mg in 4 mL (10mg/mL concentrate for IV infusion) 1 x 4 mL vial</p> <p>100 mg/10 mL injection (10mg/mL concentrate for IV infusion) 1 x 10 mL vial</p> <p>Opdivo®</p> <p>Bristol-Myers Squibb Australia Pty Ltd</p> <p>Change to listing</p> <p>(Major Submission)</p>	Metastatic renal cell carcinoma	Authority Required (STREAMLINED) listing for treatment of advanced or metastatic clear cell variant renal cell carcinoma.	The PBAC did not recommend that nivolumab be listed on the PBS for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) based on unacceptable and uncertain cost-effectiveness at the requested price. The PBAC recognised the clinical need for nivolumab in this relatively rare cancer. Based on data presented from a randomised, open-label, phase 3 study of nivolumab versus everolimus, the PBAC accepted that nivolumab statistically significantly increases overall survival compared to everolimus. However, the PBAC considered that when the model was specified appropriately and used effective prices, nivolumab was unlikely to be cost-effective.
		Sponsor comment:	The sponsor is disappointed with the outcome, however is committed to working with the PBAC to ensure nivolumab is available to Australian patients for the treatment of RCC via the PBS in the earliest possible timeframe.

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<p>OLAPARIB</p> <p>50mg capsule, 4 x 112 capsules</p> <p>Lynparza™</p> <p>AstraZeneca Pty Ltd</p> <p>Matters Outstanding</p> <p>(Minor Submission)</p>	<p>Ovarian, fallopian tube or primary peritoneal cancer</p>	<p>Resubmission for an Authority Required (STREAMLINED) listing for the treatment of platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high-grade serous features or a high grade serous component.</p>	<p>The PBAC did not recommend the listing of olaparib for the treatment of high grade serous ovarian, fallopian tube, or primary peritoneal cancer on the basis that the economic model presented did not align with the observed results of the clinical trial. The overall survival benefit was therefore significantly overestimated in the model and, once this is corrected, the cost effectiveness would be unacceptable.</p>
		<p>Sponsor comment:</p>	<p>The sponsor had no comment.</p>
<p>PERAMPANEL</p> <p>2 mg tablet, 7</p> <p>4 mg tablet, 28</p> <p>6 mg tablet, 28</p> <p>8 mg tablet, 28</p> <p>10 mg tablet, 28</p> <p>12 mg tablet, 28</p> <p>Fycompa®</p> <p>Eisai Australia Pty Limited</p> <p>Change to listing</p> <p>(Major Submission)</p>	<p>Epilepsy</p>	<p>Authority Required (STREAMLINED) for treatment of epilepsy with Primary Generalised Tonic-Clonic seizures.</p>	<p>The PBAC did not recommend the listing of perampanel for treatment of primary generalised tonic-clonic (PGTC) seizures, on the basis of a lack of clinical data for use in the relevant PBS population and unknown cost-effectiveness.</p> <p>In making this recommendation, the PBAC acknowledged the clinical need for additional therapeutic options for patients whose symptoms are not well controlled with the treatments currently available. The PBAC considered that the submission's analysis of perampanel as a last-line therapy (i.e. against placebo) was not an appropriate reflection of its likely place in therapy (as an additional option for refractory patients) and noted that the evidence provided in the submission did not address the refractory population.</p> <p>Given their view on the appropriate clinical place for perampanel, the PBAC considered that the submission's nomination of placebo as the comparator was not appropriate. Therefore the clinical and economic analyses presented in the submission were not informative to the consideration of the comparative efficacy and cost-effectiveness of perampanel in the relevant PBS population.</p>
		<p>Sponsor comment:</p>	<p>The sponsor had no comment.</p>

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<p>TALIMOGENE LAHERPAREPVEC</p> <p>1 million PFU/mL solution for injection, 1 x 1 mL vial</p> <p>Imlygic®</p> <p>Amgen Australia Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	<p>Melanoma</p>	<p>Authority Required listing for treatment of Unresectable Stage III or Stage IV melanoma without visceral metastases.</p>	<p>The PBAC did not recommend the listing of talimogene laherparepvec (T-VEC) on the basis of highly uncertain magnitude of clinical benefit, and thus highly uncertain cost effectiveness compared to its nominated comparators (pembrolizumab, nivolumab and ipilimumab). The PBAC acknowledged that there may be some short-term unmet clinical need for additional therapies beyond current PBS-subsidised medicines in a small subgroup of previously untreated patients with stage IIIb/c and stage IVM1a melanoma. However, the PBAC considered that the comparative effectiveness and safety of T-VEC versus its comparators could not be determined with sufficient confidence using the data presented in the submission.</p>
		<p>Sponsor comment:</p>	<p>Despite a number of promising melanoma therapies recently being recommended by the PBAC, Australia still has one of the highest incidences of melanoma in the world and there remains a clinical need for alternative treatment options. Talimogene laherparepvec (IMLYGIC) is effective and well tolerated while offering a new and different mode of action that provides a useful addition to existing therapies. Amgen looks forward to continuing to work with the PBAC to ensure that Australian patients with melanoma are able to access treatment with talimogene laherparepvec.</p>

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<p>TENOFOVIR with EMTRICITABINE</p> <p>tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg tablet, 30</p> <p>Truvada®</p> <p>Gilead Sciences Pty Ltd</p> <p>Change to listing</p> <p>(Major Submission)</p>	<p>Human immunodeficiency virus (HIV) pre-exposure prophylaxis</p>	<p>Authority Required listing to reduce the risk of sexually acquired HIV infection in adults at substantial risk of HIV infection.</p>	<p>The PBAC did not recommend the listing of Truvada for HIV pre-exposure prophylaxis (PrEP) on the basis of unacceptable and uncertain cost effectiveness in the proposed population and at the proposed price. The PBAC considered that the cost-effectiveness estimates were unreliable and that attempts to restrict the eligible population by quantifying an individual's future risk of HIV infection based on self-reported future behaviour, and limiting access to those with a predicted annual risk of infection of 3% or higher, may not be feasible or acceptable to clinicians and consumers. The PBAC considered it may be more appropriate for a broader group of individuals to have access to Truvada as PrEP, for example all individuals for whom clinician and consumer judge the potential benefit to outweigh the risk. The PBAC noted that in order to make Truvada available for PrEP to the whole 'at risk' population a substantial reduction in price would be needed to achieve cost effectiveness.</p> <p>In making its decision the PBAC noted that, based on the evidence provided, pre-exposure prophylaxis could reduce the risk of acquiring HIV when used in combination with safer sex practices and regular HIV testing, but as a strategy PrEP was not always effective in preventing the acquisition of the virus. The PBAC noted that the efficacy of Truvada was highly dependent on adherence, and that it is not clear if subjects at high risk of contracting HIV due to self-reported low adherence to safer sex practices would also have lower adherence to medication.</p> <p>The PBAC considered that the economic models presented were unlikely to provide a reliable estimate of the true cost effectiveness of Truvada in the requested population. The base case incremental cost-effectiveness ratio (ICER) estimated based on the costs and consequences of treating an average individual at high risk of HIV infection (in the range \$105,000-\$200,000/QALY) was unacceptably high and uncertain. The cost savings (and hence dominant ICER) when incorporating the impact on the broader population were considered unlikely to be realised. A number of issues were noted with the model inputs and structure, and the results were considered to lack face validity.</p>

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		Sponsor comment:	The submission sought a listing consistent with the TGA indication, using the WHO recommendation for PrEP suitability to identify the eligible population, but notes the PBAC's considerations regarding defining the eligible population. The Sponsor is committed to working with the PBAC towards the future listing of Truvada for PrEP.
<p>ULIPRISTAL</p> <p>5 mg tablet, 28</p> <p>Esmya®</p> <p>Vifor Pharma Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	Moderate to severe symptoms of uterine fibroids	Authority Required (STREAMLINED) listing for treatment of moderate to severe symptoms of uterine fibroids.	<p>The PBAC decided not to recommend that ulipristal be listed on the PBS for the treatment of moderate to severe uterine fibroids on the basis that:</p> <ul style="list-style-type: none"> • the clinical place of treatment was not adequately established, • the nominated comparator, goserelin, is not PBS listed for the treatment of uterine fibroids and its use in clinical practice was not substantiated, • the comparative effectiveness and safety of ulipristal compared to goserelin was not established, and • no evidence was presented assessing the impact of ulipristal on surgical outcomes. <p>The submission included separate sets of studies of ulipristal and goserelin that did not allow for a direct or an indirect comparison of ulipristal versus goserelin to be conducted. The PBAC agreed that there was a possible clinical place for ulipristal in the short-term treatment of moderate to severe uterine fibroids prior to surgery and that this use was supported by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.</p>
		Sponsor comment:	Vifor Pharma believes there is a clinical place for ulipristal acetate in the Australian healthcare system and will continue to present the available evidence to demonstrate the cost-effectiveness of treating moderate to severe symptoms of uterine fibroids to the PBAC.