

**MARCH 2017 PBAC MEETING PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND**

<b>DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION</b>	<b>TGA INDICATION</b>	<b>CURRENT PBS LISTING</b>	<b>LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION</b>	<b>PBAC OUTCOME</b>
<p>APREMILAST</p> <p>Tablet 30 mg Pack containing 4 tablets 10 mg, 4 tablets 20 mg and 19 tablets 30 mg</p> <p>Otezla®</p> <p>Celgene Pty Ltd</p> <p>(Minor Submission)</p>	<p>Apremilast is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients; and the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.</p>	<p>Apremilast is not currently PBS listed</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for treatment of patients with moderate to severe plaque psoriasis.</p> <p>Comparator: Cyclosporin.</p> <p>Clinical claim: Superior efficacy and safety compared with cyclosporin.</p> <p>Economic claim: Cost utility analysis based on non-randomised persistence data from United States longitudinal claims data.</p> <p>Sponsor's comments:</p>	<p>The PBAC did not recommend the listing of apremilast for the treatment of patients with moderate-to-severe plaque psoriasis who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate.</p> <p>The PBAC recalled it previously accepted cyclosporin as the main comparator. The minor resubmission did not change the comparator.</p> <p>The PBAC noted that the previous submission failed to provide a sufficient basis to support the claim of superior effectiveness and safety compared with cyclosporin. The minor resubmission did not address these concerns.</p> <p>The PBAC considered that as its concerns with the claim of superior effectiveness and safety had not been addressed, the minor resubmission did not present a basis on which to recommend apremilast on a cost-effectiveness basis, compared with cyclosporin. The PBAC noted that the minor resubmission requested a reduced price for apremilast but did not address its previous concerns regarding the economic model.</p> <p>Celgene believes apremilast has significant advantages over Cyclosporin and will continue to work with the Department of Health and the PBAC to achieve a positive outcome.</p>
<p>BRIVARACETAM</p> <p>Tablet 25 mg Tablet 50 mg Tablet 75 mg Tablet 100 mg Oral suspension 10 mg per mL, 300 mL</p> <p>Briviact®</p>	<p>Brivaracetam is indicated as add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy.</p>	<p>Brivaracetam is not currently PBS listed</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for treatment of partial epileptic seizures.</p>	<p>The PBAC did not recommend the listing of brivaracetam for the treatment of intractable partial epileptic seizures on the basis of a lack of a comparison with levetiracetam, or other similarly listed anti-epileptic drugs (AEDs), which the PBAC considered would be replaced by brivaracetam. The PBAC noted the resubmission proposed listing brivaracetam as third-line adjunctive therapy for use in the same population eligible for lacosamide and perampamil, however considered this was not well justified and that earlier use of brivaracetam was clinically appropriate.</p>

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<p>UCB Australia Pty Ltd</p> <p>New Listing</p> <p>(Major Submission)</p>				<p>The PBAC noted and welcomed consumer comments received relating to this submission and recognised the support for subsidised access to brivaracetam.</p>
			<p>Comparator: lacosamide.</p>	<p>The PBAC considered uncertainty remained around the appropriate comparator due to uncertainty around the place in therapy of brivaracetam in clinical practice. The PBAC reiterated its view from July 2016 that a comparison versus second-line anti-epileptic medicines, such as levetiracetam, lamotrigine or topiramate would be more appropriate.</p>
			<p>Clinical claim: Non-inferior comparative efficacy and safety compared to lacosamide.</p>	<p>The PBAC considered that the clinical evidence presented in the resubmission did not adequately address issues raised by the PBAC at its July 2016 meeting. The PBAC noted that the concerns of comparing the brivaracetam and lacosamide trials remained. The PBAC also noted no new comparative safety data were presented in the resubmission and the issues regarding the known psychological issues when brivaracetam is used with other AEDs remained.</p>
			<p>Economic claim: Cost-minimisation analysis compared to lacosamide.</p>	<p>The PBAC considered that a cost-minimisation analysis versus levetiracetam and other similarly listed AEDs would be more informative.</p>
			<p>Sponsor's comments:</p>	<p>The sponsor had no comment.</p>
<p>NIVOLUMAB with IPILIMUMAB</p> <p>Nivolumab: Injection concentrate for I.V. infusion 40 mg in 4 mL Injection concentrate for I.V. infusion 100</p>	<p>Nivolumab, in combination with ipilimumab, is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic</p>	<p>Nivolumab and ipilimumab are not currently PBS listed for combination therapy.</p>	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) listing for the treatment of patients with unresectable metastatic melanoma.</p>	<p>The PBAC did not recommend listing concurrent use of nivolumab and ipilimumab for the treatment of unresectable Stage III or Stage IV malignant melanoma. In reaching this conclusion, the PBAC reiterated its previous view that the use of this combination was associated with a modest improvement in progression-free survival, but also a substantial increase in adverse events, and had not adequately demonstrated any advantage in terms of either quality of life or overall</p>

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<p>mg in 10 mL Ipilimumab: Injection concentrate for I.V. infusion 50 mg in 10 mL Injection concentrate for I.V. infusion 200 mg in 40 mL</p> <p>Opdivo® with Yervoy®</p> <p>Bristol-Myers Squibb Australia Pty Ltd</p> <p>Change to Listing (Major Submission)</p>	<p>dehydrogenase (LDH).</p>			<p>survival.</p>
			<p>Comparator: the treatment sequence of PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon disease progression.</p>	<p>Although the PBAC considered that this was an appropriate comparator, it noted that there was no direct randomised trial evidence presented for the comparison. The PBAC viewed that the best available evidence for an appropriate comparison was the CA209-067 trial.</p>
			<p>Clinical claim: Superior efficacy and inferior safety compared to nivolumab followed by ipilimumab monotherapy.</p>	<p>The CA209-067 trial supported a claim for superior effectiveness in terms of an approximately 4.8 months increase in median progression-free survival, but the PBAC was not convinced that this gain had a clinically meaningful benefit with regard to estimating any effect on quality of life or predicting any effect on overall survival. The claim of inferior safety was reasonable. For every 100 patients treated with nivolumab and ipilimumab in comparison to nivolumab monotherapy over a minimum duration of follow-up of 9 months:</p> <ul style="list-style-type: none"> <li>• approximately 39 additional patients would experience a Grade 3 or higher treatment-related severe AE;</li> <li>• approximately 29 additional patients would experience a treatment-related AE leading to discontinuation of treatment.</li> </ul>
			<p>Economic claim: cost-utility analysis of nivolumab and ipilimumab followed by best supportive care (BSC) upon disease progression compared with nivolumab monotherapy followed by ipilimumab monotherapy upon disease progression.</p>	<p>The PBAC considered that the resubmission's model presented an unacceptably high and uncertain ICER in excess of \$200,000/QALY, and thus failed to demonstrate acceptable cost-effectiveness. The committee was concerned that the model results bore little relation to the observed trial data, that it did not appropriately account for post-progression therapies, that it did not input reasonable utility values (as a measure of quality of life), and that its two year time horizon excluded consideration of long-term differences in PFS and possibly in OS.</p>
			<p>Sponsor's comments:</p>	<p>The sponsor looks forward to continuing to work with the government to provide access to this treatment option</p>

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				for melanoma patients.
<p>SELEXIPAG</p> <p>Tablet 200 mcg Tablet 400 mcg Tablet 600 mcg Tablet 800 mcg Tablet 1000 mcg Tablet 1200 mcg Tablet 1400 mcg Tablet 1600 mcg</p> <p>Upravi®</p> <p>Actelion Pharmaceuticals Australia Pty Ltd</p> <p>New Listing (Major Submission)</p>	<p>Selexipag is indicated for the treatment of idiopathic pulmonary arterial hypertension; heritable pulmonary arterial hypertension; pulmonary arterial hypertension associated with connective tissue disease; pulmonary arterial hypertension associated with congenital heart disease with repaired shunts; pulmonary arterial hypertension associated with drugs and toxins; in patients with WHO functional class II, III or IV symptoms</p>	<p>Selexipag is not currently PBS listed</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required listing as an add-on therapy for the treatment of pulmonary arterial hypertension.</p>	<p>The PBAC did not recommend the listing of selexipag for the treatment of pulmonary arterial hypertension on the basis of uncertain effectiveness and unacceptable high to very high incremental cost-effectiveness ratios (ICERs) for each of the presented surrogate outcomes.</p> <p>The PBAC noted that this resubmission provided re-analyses of the clinical data presented in the original submission, but the re-analyses did not change the PBAC's view of the cost-effectiveness of selexipag.</p>
			<p>Comparator: placebo.</p>	<p>The PBAC accepted placebo as the comparator.</p>
			<p>Clinical claim: superior comparative efficacy and inferior comparative safety compared with placebo.</p>	<p>The PBAC accepted that selexipag was likely to be superior to placebo in terms of comparative effectiveness, but that the magnitude and clinical relevance of any benefit remained unclear. The PBAC accepted the claim of inferior comparative safety compared to placebo.</p>
			<p>Economic claim: trial-based cost-effectiveness analysis.</p>	<p>The PBAC considered that the ICERs presented in the resubmission were difficult to interpret and were likely too high to support the cost-effectiveness of selexipag in the requested listing.</p>
			<p>Sponsor's comments:</p>	<p>Actelion is disappointed that the PBAC did not recommend listing of Upravi on the PBS. Actelion will seek advice from the PBAC to understand why the ICERs are perceived to be too high given that the ICERs presented for Upravi were lower than those applying for products that are currently PBS-listed. Despite a broad TGA indication, the greatest unmet medical need for Upravi is in triple combination with a PDE-5i and an ERA.</p> <p>Actelion's re-submission proposed a practical solution</p>

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<p>TRIFLURIDINE WITH TIPIRACIL</p> <p>Tablet containing 15 mg trifluridine with 6.14 mg tipiracil (as hydrochloride) Tablet containing 20 mg trifluridine with 8.19 mg tipiracil (as hydrochloride)</p> <p>Lonsurf®</p> <p>Servier Laboratories (Australia) Pty Ltd</p> <p>New Listing</p> <p>(Minor Submission)</p>	<p>A positive TGA Delegate's Overview was provided but the final indication of the TGA registration is not known.</p>	<p>Trifluridine with tipiracil is not currently PBS listed</p>	<p>A resubmission to request an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer.</p> <p>Comparator: best supportive care (BSC)</p> <p>Clinical claim: superior efficacy and inferior safety of trifluridine/tipiracil compared with BSC.</p> <p>Economic claim: cost-utility analysis of trifluridine/tipiracil.</p> <p>Sponsor's comments:</p>	<p>for the current lack of PBS funding for double combination therapy which is a requirement for a product to be used in triple combination.</p> <p>The PBAC did not recommend the listing of trifluridine with tipiracil on the PBS for treatment of patients with metastatic colorectal cancer (mCRC) who have been treated previously with or are not considered suitable for currently available therapies on the basis of a modest clinical benefit, moderate toxicity and an unacceptably high and uncertain incremental cost-effectiveness ratio given the extent of benefit observed in the trial setting may not be realised in clinical practice.</p> <p>Accepted</p> <p>The PBAC accepted the claim of superior comparative effectiveness and inferior safety. However the PBAC considered the magnitude of benefit to be modest.</p> <p>The PBAC noted that while the economic model partitioned overall survival based on progression and applied utility values (a measure of quality of life) relevant to metastatic colorectal cancer as advised by the PBAC at its November 2016 meeting, the incremental cost-effectiveness ratio remained unacceptably high.</p> <p>The sponsor had no comment.</p>
<p>ULIPRISTAL</p> <p>Tablet 5 mg</p> <p>Esmya®</p> <p>Vifor Pharma Pty Ltd</p>	<p>Ulipristal is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age</p>	<p>Ulipristal is not currently PBS listed</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for the treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age.</p>	<p>The PBAC did not recommend the listing of ulipristal on the PBS for the treatment of moderate to severe symptoms of uterine fibroids prior to planned surgery on the basis that the clinical place in therapy was unclear due to the impact of treatment on surgical outcomes versus placebo (no treatment) being unknown and the benefits in terms of symptom control compared with currently used alternatives not being assessed.</p>

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New Listing (Major Submission)			Comparator: Placebo (no treatment).	Accepted. However, the PBAC also noted the benefits claimed in the resubmission related to (i) facilitating less invasive surgery and (ii) reduced symptoms in the 3 month period prior to surgery. For the benefit relating to surgery the PBAC reiterated its previous advice that placebo is the appropriate comparator. In terms of reducing symptoms the PBAC noted that alternative treatments such as tranexamic acid, nonsteroidal anti-inflammatory (NSAI) drug, oral contraceptive pills and intrauterine devices (IUDs) are used in the clinical practice. These treatments were not considered in the submission.
			Clinical claim: ulipristal is superior in terms of comparative effectiveness to placebo as a proxy for an equivalent period of conservative management, with an acceptable and comparable safety and tolerability profile.	The PBAC considered the claim of superior comparative effectiveness of ulipristal over placebo was reasonable for the outcomes of controlling abnormal uterine bleeding and reducing both fibroid and uterine volume. The PBAC considered the claim of superior effectiveness was not adequately supported for the quality of life outcomes and surgery outcomes (such as surgery rates or types of surgery performed). The PBAC considered the claim of non-inferior comparative safety was not adequately supported by the data.
			Economic claim: cost-utility analysis compared with placebo.	The PBAC considered that due to a range of issues with the economic model, the PBAC was unable to judge the cost-effectiveness of the submission's proposed listing
			Sponsor's comments:	Whilst Vifor Pharma is disappointed with the decision to reject Ulipristal 5mg for a second time, we remain committed to ensuring this important medicine is made available in some way to Australian patients with moderate to severe symptoms of uterine fibroids.