

NOVEMBER 2016 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>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>New listing</p> <p>(Major 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 the treatment of moderate to severe plaque psoriasis.</p> <p>Comparator: Cyclosporin</p> <p>Clinical Claim: Superior efficacy and safety compared with cyclosporin</p>	<p>The PBAC did not recommend the listing of apremilast for moderate to severe plaque psoriasis on the basis that the evidence presented did not support the claims of superior comparative efficacy or safety versus cyclosporin and the cost effectiveness of apremilast was uncertain and unacceptable at the requested price.</p> <p>The PBAC noted and welcomed the consumer comments received relating to this submission. The PBAC recognised the support for subsidised access to apremilast.</p> <p>The PBAC noted that the estimated net cost of apremilast to government was more than \$100 million in four of the first five years of listing.</p> <p>The sponsor requested that if methotrexate was considered a relevant comparator, that apremilast be restricted to patients who have failed treatment with methotrexate. In this context, the PBAC accepted cyclosporin as the main comparator.</p> <p>The PBAC recalled that the March 2015 submission had described apremilast as non-inferior in terms of effectiveness and superior in terms of safety compared with cyclosporin, and that it previously considered that neither of these claims had been adequately supported.</p> <p>The resubmission revised the clinical claim to describe apremilast as superior in terms of comparative effectiveness and safety compared with cyclosporin based on a real-world, non-randomised US study of comparative persistence rates.</p> <p>The PBAC considered that the applicability of the non-randomised US persistence data presented in the submission to the likely PBS use of apremilast was</p>

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				<p>unclear and the submission did not demonstrate that apremilast was associated with improvements in health outcomes relevant to psoriasis (compared with cyclosporin). In this regard, the PBAC noted that the indirect comparison of clinical trial evidence suggested that there is no statistically significant difference in the proportion of patients achieving PASI 75 response at 16 weeks for apremilast versus 10 weeks for cyclosporin.</p> <p>Overall, the PBAC considered that the non-randomised persistence data was relevant supportive information, but that it was an insufficient basis to support the claim of superior comparative effectiveness and safety.</p>
			<p>Economic Claim: Cost utility analysis based on non-randomised persistence data from United States longitudinal claims data</p>	<p>Given that the economic model used non-randomised persistence data as an unsubstantiated proxy for the comparative effectiveness and safety of apremilast and cyclosporin, the PBAC considered the model to be uninformative for decision making. Notwithstanding this issue, the PBAC considered the ICER per QALY gained for apremilast was uncertain and unacceptably high.</p>
			<p>Sponsor comment:</p>	<p>Celgene is disappointed with the outcome given the acknowledged clinical place for apremilast as a treatment option for plaque psoriasis. Celgene will continue to work with the Department to exhaust all feasible options with the PBAC and Department to make apremilast available to Australian patients.</p>

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<p>CETUXIMAB</p> <p>Injection 100 mg in 20 mL Injection 500 mg in 100 mL</p> <p>Erbitux®</p> <p>Merck Serono Australia Pty Ltd</p> <p>New listing</p> <p>(Minor Submission)</p>	<p>Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer; and for the treatment of patients with squamous cell cancer of the head and neck.</p>	<p>Cetuximab is currently PBS listed for treatment of metastatic colorectal cancer and Stage III, Stage IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx.</p>	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (RM SCCHN).</p>	<p>The PBAC decided not to recommend cetuximab in combination with platinum chemotherapy for previously untreated RM SCCHN on the basis of uncertain clinical effectiveness and uncertain and unfavourable cost-effectiveness.</p>
			<p>Comparator: Platinum-based chemotherapy</p>	<p>Accepted.</p>
			<p>Clinical Claim: superior efficacy, with an inferior but manageable safety profile compared to chemotherapy alone</p>	<p>The PBAC reaffirmed its conclusion from the March 2016 meeting that the incremental benefits with cetuximab plus chemotherapy over chemotherapy alone in the treatment of RM SCCHN were small, and that the addition of cetuximab increased toxicity.</p>
			<p>Economic Claim: cost-utility analysis for the ITT population of the EXTREME trial against chemotherapy alone</p>	<p>The PBAC considered the cost per quality adjusted life year gained of \$75,000-\$105,000 to be high and uncertain, reflecting the uncertain extent of clinical benefit. The PBAC also noted that the economic model did not address all of the issues identified at its March 2016 meeting, including the choice of extrapolation method, the source of the utility values, and the optimistic time horizon.</p>
<p>Sponsor comment:</p>	<p>Merck is disappointed with a second rejection by the PBAC. Overseas, cetuximab has been the standard of care for patients with RM SCCHN for many years as recommended in European and American Guidelines. We shall discuss with the Department to determine if there is a way forward.</p>			

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<p>HIGHLY PURIFIED HUMAN MENOPAUSAL GONADOTROPHIN</p> <p>Powder for injection, 600 I.U Powder for injection, 1200 I.U</p> <p>Menopur®</p> <p>Ferring Pharmaceuticals Pty Ltd</p> <p>New listing (Minor Submission)</p>	<p>Gonadotrophin is indicated for the treatment of anovulatory infertility, including polycystic ovarian disease in women who have been unresponsive to treatment with clomiphene citrate; and controlled ovarian hyperstimulation as part of assisted reproductive technologies (ART).</p>	<p>Human menopausal gonadotrophin is currently PBS listed for Assisted Reproductive Technology under Section 100 (IVF).</p>	<p>Resubmission to request a restricted benefit listing for anovulatory infertility.</p>	<p>The PBAC decided not to recommend the PBS listing of HP-hMG for the treatment of anovulatory infertility on the basis that the minor resubmission did not adequately support a claim of non-inferiority to follitropin alfa.</p>
			<p>Comparator: follitropin alfa</p>	<p>Accepted</p>
			<p>Clinical Claim: non-inferior effectiveness and safety compared with follitropin alfa.</p>	<p>The PBAC recalled that in March 2016 it rejected a major submission for HP-hMG on the basis that the evidence presented did not adequately support a claim of non-inferiority to the comparator, follitropin alfa. The PBAC considered that as no new clinical trial data had been provided in the resubmission, there was an insufficient basis on which to change its previous consideration regarding the claim of non-inferiority to follitropin alfa.</p>
			<p>Economic Claim: Cost-minimisation analysis with equi-effective dose ratio of 1 IU and 1.14 IU.</p>	<p>The PBAC noted that reliable equi-effective doses could not be estimated from the CS002 trial as the trial did not adequately demonstrate non-inferiority of HP-hMG and follitropin alfa. Notwithstanding this, the PBAC considered the equi-effective dose ratio proposed in the minor resubmission of 1:1.14 was not adequately supported as it was based on the analysis of the per-protocol population. Based on the analysis of the intention-to-treat population the equi-effective dose ratio was noted to be higher (1:1.32 to 1:1.46).</p>
<p>Sponsor comment:</p>	<p>Ferring is disappointed with this PBAC decision however we will continue to work with physicians, patients and the PBAC to find a way to make ovulation induction with MENOPUR available on the PBS as a treatment option for patients with anovulatory infertility.</p>			

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<p>IBRUTINIB</p> <p>Capsule 140 mg</p> <p>Imbruvica®</p> <p>Janssen-Cilag Pty Ltd</p> <p>New listing</p> <p>(Minor submission)</p>	<p>Ibrutinib is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in patients who have received at least one prior therapy, or as first line in CLL patients with 17p deletion; and mantle cell lymphoma (MCL) in patients who have received at least one prior therapy.</p>	<p>Ibrutinib is not currently PBS listed.</p>	<p>Re-submission to request Authority Required (STREAMLINED) listing for the treatment of relapsed or refractory CLL and relapsed or refractory SLL.</p>	<p>The PBAC did not recommend the listing of ibrutinib for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). Although the new submission proposed a reduction in the total expenditure caps for ibrutinib compared to the previous submission, and although that reduction would effectively reduce the incremental cost per quality adjusted life year (QALY) gained, the PBAC considered that, in the event that usage exceeded the level of the new caps, the cost-effectiveness of treatment remained unacceptably high and uncertain.</p>
			<p>Comparator: Rituximab plus chlorambucil</p>	<p>Accepted</p>
			<p>Clinical Claim: superior efficacy profile compared to ofatumumab (and by extension chlorambucil plus rituximab, the main comparator) and a different but acceptable safety and tolerability profile.</p>	<p>The PBAC recalled its previous clinical advice that ibrutinib is an effective treatment for CLL and SLL based on the results of the RESONATE trial as monotherapy for patients who meet certain criteria.</p>
			<p>Economic Claim: Cost-utility analysis of ibrutinib verses rituximab plus chlorambucil.</p>	<p>The PBAC considered that at the effective incremental cost per QALY gained with the proposed expenditure caps the cost-effectiveness of treatment remained unacceptably high and uncertain. Additionally, the PBAC remained of the view that, at a total net cost to the PBS of more than \$100 million over the first 5 years of listing ibrutinib, there would be a significant opportunity cost to the Commonwealth.</p>
			<p>Sponsor comment:</p>	<p>Janssen is disappointed that the submission was rejected. We remain concerned that the multiple conservative assumptions required by the PBAC underestimates the benefit and value of ibrutinib. The requirements of the PBAC for a truncated time horizon with the additional requirement of convergence, the</p>

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				<p>exclusion of adjustment for cross-over and the adjustment of the comparator arm contrast significantly with comparable HTA agencies including NICE.</p> <p>Janssen maintains that ibrutinib is a cost-effective treatment at the proposed price and under the terms of the proposed RSA provided budget certainty to the Commonwealth. Janssen are engaging with the PBAC to work towards a resolution.</p>
<p>LANREOTIDE</p> <p>Injection 60 mg (as acetate) in single dose pre-filled syringe Injection 90 mg (as acetate) in single dose pre-filled syringe Injection 120 mg (as acetate) in single dose pre-filled syringe</p> <p>Somatuline® Autogel®</p> <p>Ipsen Pty Ltd</p> <p>Change to listing (Major Submission)</p>	<p>Lanreotide is indicated for the treatment of acromegaly when circulating levels of growth hormone and IGF-1 remain abnormal after surgery and/or radiotherapy or in patients who are dopamine agonist treatment refractory; symptoms of carcinoid syndrome associated with carcinoid tumours; and gastroentero-pancreated neuroendocrine tumours (GEP-NETs) in adult patients with unresectable locally advanced or metastatic disease.</p>	<p>Lanreotide is currently PBS listed for the treatment of acromegaly and functional carcinoid tumour.</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing for the treatment of non-functional GEP-NETs in adult patients with unresectable locally advanced or metastatic disease.</p>	<p>The PBAC did not recommend the listing of lanreotide for the treatment of non-functional GEP NETs on the basis of unfavourable and uncertain cost-effectiveness at the price proposed by the sponsor.</p> <p>The PBAC acknowledged and welcomed the many consumer comments received from people living with non-functional GEP-NETs and the input from the Unicorn Foundation. In addition, representatives of the PBAC met with the Unicorn Foundation prior to the PBAC meeting to discuss the clinical place, benefits and side effects of lanreotide for the requested patient population. The Committee recognised the strong support for subsidised access to lanreotide for this condition.</p> <p>The PBAC recalled that in November 2015 it considered that the requested restriction for lanreotide for non-functional GEP-NETs should be tightened and include criteria to identify patients who would be more likely to benefit from active treatment (i.e. unsuitable for watchful waiting). The PBAC considered that there was a clinical place for lanreotide in a small, well selected patient population. However, the PBAC considered that the restriction proposed in the resubmission did not clearly identify this population. The PBAC noted that it</p>

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				<p>was not possible to identify patients most suitable for treatment with lanreotide for non-functional GEP-NETs based on biomarkers or symptoms and that PBS restrictions are not intended to guide clinical practice. Accordingly, the PBAC considered it may be more appropriate to leave the judgement of suitability for active treatment to clinicians.</p>
			<p>Comparator: Watchful waiting/ placebo</p>	<p>Accepted.</p>
			<p>Clinical Claim: Superior efficacy in progression free survival (PFS) and non-inferior or inferior safety for lanreotide compared with placebo.</p>	<p>The PBAC considered the efficacy of lanreotide to be superior in relation to progression free survival (hazard ratio 0.47, 95% CI 0.30, 0.73) but that the clinical significance of the PFS results remained uncertain, as radiologic progression may not necessarily be accompanied by a change in symptoms. The PBAC recalled that the clinical data from the CLARINET trial did not support a difference in overall survival between treatment arms and noted the resubmission was no longer claiming a survival advantage.</p> <p>The PBAC considered lanreotide to be inferior compared with placebo in terms of safety. The PBAC noted that on the basis of the direct evidence presented in the resubmission, every 100 patients treatment with lanreotide, compared with placebo (for watchful waiting) resulted in approximately:</p> <ul style="list-style-type: none"> • 17 additional patients experiencing gastrointestinal disorders; • 7 patients experiencing injection site pain; and • 12 additional patients experiencing cholelithiasis (gallstones). <p>Overall, the PBAC considered that there was likely to be a clinically meaningful, anti-proliferative benefit</p>

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				<p>associated with treatment with lanreotide, which would outweigh the potential adverse events, for a small, well selected group of patients. However, the PBAC considered that not all patients with non-functional GEP-NETs would benefit from active treatment, and noted that there are no biomarkers which reliably identify those patients in whom the benefits outweigh the risks.</p>
			<p>Economic Claim: Cost-utility analysis of lanreotide versus watchful waiting (placebo)</p>	<p>The PBAC considered the assumption that all patients receive lanreotide post-progression in the economic model was inappropriate given that the requested restriction for lanreotide would allow post-progression treatment which is otherwise not PBS-subsidised for patients with non-functional GEP-NETs.</p> <p>Notwithstanding the concerns with the clinical significance of the gain in PFS and post-progression use of lanreotide, the PBAC considered that the base case incremental cost effectiveness ratio of \$75,000-\$105,000 per quality adjusted life year gained was not sufficiently cost-effective to justify a recommendation for listing.</p>
			<p>Sponsor comment:</p>	<p>Whilst Ipsen is disappointed with the decision, we remain committed to working with PBAC to ensure this important indication is made available to Australian patients with GEP-NETs.</p>

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<p>LUMACAFTOR with IVACAFTOR</p> <p>Tablet containing lumacaftor 200 mg with ivacaftor 125 mg</p> <p>Orkambi®</p> <p>Vertex Pharmaceuticals (Australia) Pty Ltd</p> <p>New listing</p> <p>(Minor Submission)</p>	<p>Lumacaftor with ivacaftor is indicated for the treatment of cystic fibrosis in patients age 12 years or older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.</p>	<p>Lumacaftor with ivacaftor is not currently listed on the PBS.</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.</p>	<p>Lumacaftor with ivacaftor was not recommended by the PBAC on the basis of unfavourable and uncertain cost-effectiveness at the requested price. The PBAC noted that the resubmission did not address the issues previously identified in its consideration of the March 2016 submission. The PBAC particularly noted the continuing uncertainty regarding long-term benefits of treatment on lung function and overall survival.</p> <p>The PBAC noted that the estimated net cost of lumacaftor/ivacaftor to government was more than \$100 million in each of the first five years of listing.</p>
			<p>Comparator: Best supportive care</p>	<p>Accepted</p>
			<p>Clinical Claim: Superior comparative effectiveness, in terms of improvements in lung function, as measured by ppFEV1, rate of pulmonary exacerbations and nutritional status, and that these outcomes are associated prolongation of life.</p>	<p>In March 2016, “the PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short term but considered that the impact of ivacaftor with lumacaftor on improvements in long-term lung function and survival was uncertain”. In addition, “the PBAC considered that the claim of equivalent comparative safety was reasonable in the short term but noted the long term safety of lumacaftor/ivacaftor is unknown.” The minor resubmission did not address these concerns.</p>
			<p>Economic Claim: Cost-utility analysis compared with best supportive care.</p>	<p>The PBAC considered that the incremental cost per quality adjusted life year gained of more than \$200,000 was unacceptably high and likely underestimated.</p>
			<p>Sponsor comment:</p>	<p>The sponsor had no comment.</p>

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<p>NIVOLUMAB</p> <p>Injection concentrate for I.V. infusion 40 mg in 4 mL</p> <p>Injection concentrate for I.V. infusion 100 mg in 10 mL</p> <p>Opdivo®</p> <p>Bristol-Myers Squibb Australia Pty Ltd</p> <p>New listing</p> <p>(Minor Submission)</p>	<p>Nivolumab is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma and locally advanced or metastatic squamous or non-squamous non-small cell lung cancer with progression on or after prior chemotherapy. Nivolumab in combination with ipilumimab is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).</p>	<p>Nivolumab is currently PBS listed for the treatment of unresectable Stage III or IV malignant melanoma.</p>	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for second-line clear cell variant renal cell carcinoma (RCC).</p>	<p>The PBAC did not recommend the listing of nivolumab for the treatment of advanced or metastatic clear cell variant RCC on grounds of unfavourable and uncertain cost-effectiveness. The PBAC considered that the benefit of treatment with nivolumab was uncertain and likely overestimated and that the proposed risk sharing arrangement would not address this uncertainty.</p>
			<p>Comparator: everolimus</p>	<p>Accepted</p>
			<p>Clinical Claim: nivolumab as superior in terms of comparative efficacy and favourable in terms of comparative safety to everolimus</p>	<p>The PBAC was satisfied that nivolumab provides, for some patients no increase in toxicity and an improvement in overall survival over everolimus however, the size of this improvement was uncertain.</p>
			<p>Economic Claim: cost utility analysis of nivolumab compared to everolimus</p>	<p>The PBAC noted that the minor resubmission addressed some, but not all of its recommendations for a respecified base case for the economic model. The PBAC considered that the assumptions and inputs to the model used to recalculate the incremental cost per quality adjusted life year gained introduced too many uncertainties to be considered reliable.</p>
			<p>Sponsor comment:</p>	<p>The sponsor remains 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.</p>

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<p>PEMBROLIZUMAB</p> <p>Powder for injection 50 mg</p> <p>Keytruda®</p> <p>Merck Sharp & Dohme (Australia) Pty Ltd</p> <p>Change to listing</p> <p>(Major Submission)</p>	<p>Pembrolizumab is indicated for the treatment of unresectable or metastatic melanoma in adults.</p>	<p>Pembrolizumab is currently PBS listed for the treatment of unresectable Stage III or Stage IV malignant melanoma.</p>	<p>Resubmission to seek PBAC reconsideration of the cost-effectiveness of pembrolizumab for the treatment of unresectable stage III or stage IV metastatic melanoma.</p>	<p>The PBAC decided not to recommend that the circumstances of the PBS listing of pembrolizumab for the treatment of unresectable Stage III or Stage IV metastatic melanoma be changed following the Managed Entry Scheme. The PBAC considered that the requested changes to the cost-effectiveness of pembrolizumab and the associated risk sharing arrangement caps contained in the Deed of Agreement were not justified, noting the primary basis for previously rejecting the increased cost per patient had not changed since the previous submission, and the numbers of eligible patients each year were likely to be overestimated.</p>
			<p>Comparator: ipilimumab</p>	<p>Since the Deed of Agreement, nivolumab has been PBS-listed for the treatment of unresectable Stage III or Stage IV metastatic melanoma on the basis that nivolumab is non-inferior to pembrolizumab and therefore is an appropriate comparator.</p>
			<p>Clinical Claim: pembrolizumab as superior in terms of comparative effectiveness and comparative safety over ipilimumab</p>	<p>The submission did not contain evidence of greater effectiveness or safety of pembrolizumab compared with nivolumab and as such could not justify a change in the circumstances of the PBS listing of pembrolizumab.</p>
			<p>Economic Claim: cost-utility analysis presenting two scenarios; a 'Deed compliant scenario' and a 'Realistic scenario' which is a multivariate sensitivity analysis of the 'Deed compliant scenario'.</p>	<p>The PBAC noted that, as nivolumab is listed on the PBS on the basis of the recommendation set out below, the cost per patient of pembrolizumab is linked to the cost per patient of nivolumab, which would remain consistent with the initial cost per patient conditions of the pembrolizumab MES:</p> <p>“The PBAC recommended that the pricing of nivolumab upon PBS listing be determined only with reference to the initial pricing conditions of the pembrolizumab MES. Any</p>

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				<p>future pricing adjustment that may be sought for pembrolizumab as part of the conditions of the pembrolizumab MES would not apply to nivolumab, thus providing the Commonwealth certainty of the nivolumab pricing. Future applications to prove cost effectiveness of nivolumab over pembrolizumab may be made at any time by the sponsor, if warranted by future clinical trial data” (paragraph 7.6, Nivolumab PSD November 2015 PBAC meeting).</p>
			<p>Sponsor comment:</p>	<p>MSD is disappointed that the superiority of pembrolizumab vs. ipilimumab hasn't been reflected.</p>