

JULY 2017 PBAC MEETING 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>LANREOTIDE</p> <p>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 gastroenteropancreatic 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 listing lanreotide on the PBS for the treatment of non-functional GEP-NETs on the basis of uncertain cost-effectiveness. The PBAC recognised from the many comments received from patients that there is strong support for subsidised access to lanreotide for this condition.</p>
			<p>Comparator: Watchful waiting/placebo</p>	<p>Accepted for first-line treatment of non-functional GEP-NETs.</p>
			<p>Clinical claim: Superior efficacy in progression free survival (PFS) and inferior safety lanreotide compared with placebo.</p>	<p>The PBAC noted that the resubmission did not present any new clinical evidence in addition to the clinical evidence from the November 2015 and November 2016 submissions. The PBAC recalled that the clinical data from the CLARINET trial did not support a difference in overall survival (OS) or quality of life between treatment arms however noted that lanreotide was associated with a statistically significant increase in radiological PFS compared with placebo (HR 0.47, 95% CI 0.30, 0.73). However, the PBAC considered that the clinical significance of the gain in PFS was unclear as radiologic progression assessed in the trial may not necessarily be directly associated with a change in clinical symptoms.</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).

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				<p>The PBAC reiterated from its previous consideration that there is likely to be a clinically meaningful, anti-proliferative benefit associated with treatment with lanreotide, which would outweigh the potential adverse events, for a small, well selected group of patients. The PBAC considered that, given the indolent and variable nature of the disease, not all patients within the broad population of patients with non-functional GEP-NETs would benefit from active treatment with lanreotide.</p>
			<p>Economic claim: Cost-utility analysis of lanreotide versus watchful waiting (placebo)</p>	<p>The PBAC considered the inputs in the economic model to estimate the cost-effectiveness of lanreotide were unreliable. Post-progression treatment sequences (based on a survey of three clinicians), costs and durations applied in the model were overestimated in favour of lanreotide. Further, the PBAC noted that resubmission did not adequately justify the rate of post-progression lanreotide use applied in the model (30% in the placebo arm and 48% in the lanreotide arm), particularly given that lanreotide is not currently PBS-subsidised for non-functional GEP-NETs.</p> <p>In addition, the PBAC noted the utility value for progressive disease (and therefore the change from the stable disease health state) used in the model was poorly supported and that estimated overall survival remained a source of uncertainty.</p> <p>Accordingly, the PBAC considered the economic model provided in the current resubmission (as well as the previous submissions) to be fundamentally unreliable for estimating the cost-effectiveness of lanreotide for the requested listing.</p> <p>The PBAC considered a significant reduction in the requested price of lanreotide would be required to provide</p>

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			Sponsor's comments	greater confidence in its cost-effectiveness. Whilst Ipsen is disappointed with the decision, we remain committed to working with the PBAC to ensure this important indication is made available to Australian patients with GEP-NETs.
<p>LIRAGLUTIDE</p> <p>Injection 6 mg/mL, 3 mL pre-filled pen</p> <p>Victoza®</p> <p>Novo Nordisk Pharmaceuticals Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	<p>Liraglutide is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:</p> <ul style="list-style-type: none"> • in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy. • in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy. • in combination therapy with basal insulin, with or without metformin. 	<p>Liraglutide is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing in combination with metformin and/or a sulfonylurea, or insulin, for the treatment of patients with T2DM under certain conditions.</p> <p>Comparator: Exenatide</p> <p>Clinical claim: The submission described liraglutide as superior in terms of comparative effectiveness over exenatide, providing a statistically significant reduction in cardiovascular risk in patients with Type 2 diabetes and high cardiovascular risk.</p> <p>Economic claim: The submission presented a modelled cost utility analysis comparing the cardiovascular benefits of liraglutide with exenatide 10 µg twice daily.</p>	<p>The PBAC did not recommend the listing of liraglutide 1.8 mg/day for treatment of patients with Type 2 diabetes mellitus and high cardiovascular risk based on inadequate clinical data and uncertain cost effectiveness. However, the PBAC reaffirmed its prior recommendation in March 2013 that accepted the non-inferiority of the effectiveness and safety of liraglutide 1.2 mg daily, when compared with exenatide 10 µg twice daily in terms of glycaemic control.</p> <p>The PBAC accepted exenatide was an appropriate comparator. However, PBAC also noted that despite not having a specific PBS listing for high CV risk patients, empagliflozin offers similar reductions in direct CV outcomes across the broader Type 2 diabetes population at a substantially lower price and may also be replaced in clinical practice.</p> <p>The PBAC considered that the claim of superior comparative effectiveness of liraglutide 1.8 mg daily for patients with type 2 diabetes mellitus at high cardiovascular risk compared with exenatide 10 µg twice daily was not adequately supported due to the lack of supporting clinical evidence that excludes the cardiovascular effects of exenatide.</p> <p>The PBAC considered that the base case economic model did not provide a reliable indication of the cost effectiveness of liraglutide versus exenatide in terms of cardiovascular risk.</p>

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			Sponsor's comments	Novo Nordisk looks forward to working with the PBAC to determine the best approach to make Victoza® available for Australians with Type 2 Diabetes who would benefit from this product.
<p>LUMACAFITOR with IVACAFITOR</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>(Major Submission)</p>	<p>ORKAMBI 200/125 is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.</p>	<p>LUMACAFITOR with IVACAFITOR is not currently PBS listed.</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 over who are homozygous for the F508del mutation in the CFTR gene.</p> <p>Comparator: Best supportive care (BSC)</p> <p>Clinical claim: The March 2016 submission claimed 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. The current resubmission claimed that the longer term data from the PROGRESS study provided further evidence that lumacaftor/ivacaftor is a disease modifying therapy which minimises the rate of deterioration over time.</p>	<p>Lumacaftor with ivacaftor was not recommended by the PBAC for listing on the PBS for the treatment of patients with cystic fibrosis (CF) aged 12 years or older who are homozygous for the F508del mutation in the CFTR gene on the basis of uncertainty around the longer term impact of lumacaftor/ivacaftor on lung function and survival beyond 2 years of treatment and unacceptable cost effectiveness at the requested price.</p> <p>Accepted</p> <p>The PBAC noted that updated evidence from the PROGRESS extension study demonstrated that the modest 2.81 percentage point improvement in ppFEV1 in lumacaftor/ivacaftor treated patients versus placebo at 24 weeks observed in TRAFFIC/TRANSPORT was not maintained after an additional 96 weeks of treatment. The PBAC considered the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the evidence presented in the resubmission.</p> <p>However, the PBAC noted that on the basis of the direct randomised trials presented by the resubmission, a patient treated with lumacaftor/ivacaftor could expect to have one fewer pulmonary exacerbation over 2.5 years, and one fewer hospitalisation due to a pulmonary exacerbation over 3 years. The PBAC therefore considered that the claim of superior comparative effectiveness was reasonable.</p>

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			Economic claim: Cost-utility analysis compared with best supportive care.	The PBAC noted that the economic model included in the resubmission was based on the assumption that lung function was maintained for patients treated with lumacaftor/ivacaftor for the remainder of their life, and this was inconsistent with the longer-term clinical evidence. Accordingly, the PBAC defined a scenario which it considered more informative for decision making, by changing inputs to the resubmission's economic model to better reflect the available clinical data. This scenario resulted in an unacceptably high incremental cost effectiveness ratio (ICER) of significantly more than \$1,000,000 per quality adjusted life year (QALY) gained.
			Sponsor's comments	The Sponsor is extremely disappointed in this decision which we believe is based on unreasonable assumptions that severely undervalue the long term systemic benefits of lumacaftor + ivacaftor. This medicine is unique in treating the underlying cause of CF - not just the symptoms - and fulfils a significant unmet need for the CF community.
<p>PRALATREXATE</p> <p>Solution for I.V. infusion 20 mg in 1 mL</p> <p>Folotyn®</p> <p>Mundipharma Pty Ltd</p> <p>New listing</p> <p>(Major Submission)</p>	<p>FOLOTYN is indicated for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy.</p>	<p>PRALATREXATE 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 peripheral T-cell lymphoma who are refractory to, or have relapsed following, first line chemotherapy.</p>	<p>The PBAC did not recommend the Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL), on the basis of inadequate evidence of improved clinical effectiveness over currently available alternative therapies, together with a high burden of adverse events, and unacceptable cost-effectiveness.</p> <p>The PBAC recalled that the previous decisions to reject pralatrexate in November 2015 and March 2016 had considered that a future major resubmission should present more robust evidence to demonstrate the comparative efficacy and safety of pralatrexate over the comparators, ideally including other evidence of clinical benefit, such as quality of life (QoL) data, a substantially</p>

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				<p>updated economic evaluation and revised financial estimates. Furthermore, noting that brentuximab for the treatment of adult patients with relapsed or refractory small anaplastic large cell lymphoma (sALCL) was accepted in the ICER range of \$45,000 to \$75,000/QALY, the PBAC had previously considered that given the uncertain clinical benefit of pralatrexate, an ICER at the lower end of this range would be needed in order for pralatrexate to be considered acceptably cost-effective. The PBAC noted these key considerations were not adequately met in the July 2017 resubmission.</p>
			<p>Comparator: Basket of treatments</p>	<p>The PBAC accepted that a basket of treatments was the appropriate the main comparator, noting that gemcitabine, vinorelbine, doxorubicin, and romidepsin were appropriate comparators for the potential use of pralatrexate in the third line setting, after progression on brentuximab or other treatments from the submission’s nominated basket of treatments in the second line. The PBAC advised that brentuximab was expected to remain the preferred choice of treatment for the sALCL subtype of PTCL and was most likely to be used prior to pralatrexate, as confirmed by the sponsor hearing for this resubmission, and therefore it was inappropriate to have included brentuximab in the nominated basket of comparators. This was reaffirmed by the fact that only one patient was treated with brentuximab in the evidence presented from historical control cohorts.</p>
			<p>Clinical claim: Superior efficacy and non-inferior safety compared with nominated basket of treatments</p>	<p>The submission compares outcomes of patients receiving pralatrexate that were prospectively accrued into a clinical trial requiring strict entry criteria and who could receive further lines of therapy after pralatrexate, with patients receiving with a range of alternative therapies treated non-contemporaneously and without strict entry criteria, and only using data from their last line of therapy. This confounding cannot be overcome fully, neither by</p>

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				<p>approaches taken in the current resubmission, nor the matched analysis used previously. The PBAC considered that the survival benefit of pralatrexate over alternative therapies has not been proven and that the incremental clinical benefits are highly uncertain. The submission's claim of superior comparative effectiveness against the nominated basket of treatments remained unsupported. The PBAC agreed that safety was overall no worse than alternative chemotherapy regimens, but that the rates of severe mucositis and discontinuations due to adverse events were substantial and indicated that the treatment had significant toxicity.</p>
			<p>Economic claim: Cost-utility analysis based on a naïve indirect comparison of pralatrexate with a basket of comparator treatments</p>	<p>The PBAC considered that although several structural improvements were incorporated in the economic model presented in this resubmission, the underlying lack of evidence to support the claim of superior efficacy resulted in unreliable inputs and optimistic extrapolations, leading to an economic model that did not provide a plausible basis for appropriately estimating the cost-effectiveness of pralatrexate.</p> <p>As such, notwithstanding the clinical need for new and effective treatments for relapsed or refractory PTCL, the PBAC remained unconvinced that pralatrexate was cost effective compared to current treatments available to patients, at the price proposed by the resubmission, which was unchanged from the previous resubmission.</p>
			<p>Sponsor's comments</p>	<p>As recognised by the PBAC, there is a clinical need for new effective treatments for the relapsed or refractory peripheral T-Cell lymphoma. Mundipharma remains committed to making pralatrexate available to patients with relapsed or refractory peripheral T-Cell lymphoma.</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>LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.</p>	<p>TRIFLURIDINE WITH TIPIRACIL is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer.</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 current available therapies. The PBAC noted the modest clinical benefit in the context of substantial toxicity, and uncertain incremental cost-effectiveness given the extent of benefit observed in the trial and model may not be realised in clinical practice.</p>
			<p>Comparator: Best supportive care (BSC)</p>	<p>Accepted</p>
			<p>Clinical claim: Superior efficacy and inferior safety of trifluridine/tipiracil compared with BSC.</p>	<p>There was no change to the clinical claim from March 2017 resubmission. The PBAC previously accepted the claim of superior comparative effectiveness and inferior safety. However the PBAC considered the magnitude of benefit to be modest.</p>
			<p>Economic claim: Cost-utility analysis of trifluridine/tipiracil.</p>	<p>The PBAC noted that the economic model incorporated a reduced price for trifluridine/tipiracil from the March 2017 resubmission. However the PBAC considered that the base case ICER presented in the submission was uncertain and that the true ICER would be higher than what would be considered cost-effective.</p>
<p>VINFLUNINE</p> <p>Solution concentrate (as ditartrate) for I.V. infusion 50 mg in 2 mL</p>	<p>Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.</p>	<p>VINFLUNINE is not currently PBS listed.</p>	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) listing for the treatment of locally advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.</p>	<p>The PBAC did not recommend listing vinflunine on the PBS for the treatment of locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU), on the basis of lack of evidence of an incremental gain in overall survival versus currently available alternative active chemotherapy. The PBAC noted that compared with best supportive care (BSC) the incremental benefit was small for both overall survival and progression free survival in the context of the significant toxicity of the</p>

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Solution concentrate (as ditartrate) for I.V. infusion 250 mg in 10mL Javlor® Pierre Fabre Medicament Australia Pty Ltd New listing (Major Submission)				drug. The PBAC concluded that the incremental cost-effectiveness ratio (ICER) was high and underestimated in the submission.
			Comparator: best supportive care (BSC) and active chemotherapy	Active chemotherapy but not best supportive care accepted as relevant comparator.
			Clinical claim: superior efficacy and inferior safety of vinflunine compared with BSC. No clinical claim was made regarding vinflunine compared to active chemotherapy.	The PBAC considered there was insufficient evidence of an incremental gain in overall survival compared with BSC. The PBAC further noted that the incremental effectiveness of vinflunine versus the relevant comparator of alternative active chemotherapy was unknown, but considered it likely to be insignificant.
			Economic claim: cost-utility analysis of vinflunine using a 'mixed' 50:50 ITT/mITT population.	The PBAC considered that use of the mixed ITT/mITT population in the economic model favoured vinflunine. The PBAC maintained its views from November 2011 and November 2015 that the ITT population is the appropriate basis for assessing the clinical and cost effectiveness of vinflunine versus BSC. The PBAC considered that the cost-effectiveness ratio for the ITT population was high and highly uncertain, given the Committee's concerns about the uncertainty in the incremental gain in overall survival of vinflunine over BSC. The PBAC noted the absence of an informative cost-utility analysis versus active chemotherapy.
			Sponsor's comments.	The sponsor had no comment.