

**July 2014 PBAC OUTCOMES - "1<sup>st</sup> 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 Recommendation
<p>ABIRATERONE, tablet, 250 mg, Zytiga®</p> <p>Janssen-Cilag Pty Ltd</p> <p>Change to listing</p> <p>(Major submission)</p>	<p>Prostate Cancer</p>	<p>Section 85 Authority required listing for abiraterone for the treatment of metastatic castration resistant prostate cancer (mCRPC) to include patients who have progressed following treatment with androgen deprivation therapy (ADT), who would not have benefit from immediate chemotherapy.</p>	<p>The PBAC rejected the submission for the following reasons:</p> <ul style="list-style-type: none"> <li>• “watchful waiting” was not considered an appropriate comparator for establishing cost-effectiveness in this setting;</li> <li>• the post-hoc subgroup analysis for defining the PBS eligible population was inadequately justified;</li> <li>• the ICERs for both the post-hoc sub group and particularly the more appropriate ITT population were unacceptably high; and</li> <li>• the total PBS cost of treatment with abiraterone shifting from post-docetaxel to post-ADT was uncertain.</li> </ul> <p>The PBAC also noted comments from clinicians that for a small number of patients the current abiraterone restriction, requiring failure of, or intolerance to, docetaxel is a hurdle in gaining access to treatment where a single administration of docetaxel would inevitably demonstrate the patient was intolerant to docetaxel. PBAC considered a solution may be to amend the current restriction to allow PBS subsidised abiraterone where a patient is considered “unsuitable for docetaxel treatment on the basis of demonstrated or predicted intolerance to docetaxel”. PBAC considered this to be a minor change that may provide access to a small number of patients who are currently disadvantaged by the requirement to demonstrate intolerance. The proposed amendment of the restriction would not expand the market and would be adequately dealt with under existing risk share arrangements.</p> <p>On the basis of direct evidence presented by the submission, the comparison of abiraterone + prednisolone/prednisone and placebo + prednisolone/prednisone resulted in an improvement of approximately 5 months overall survival and 8 months progression free survival for the intention to treat (ITT) population. While this did not meet statistical significance based on the strict pre-specified significance criteria, this result may have been affected by the early termination and crossover observed in the trial. For every 100 patients treated with abiraterone, in comparison with placebo, approximately 7 additional patients experienced hepatotoxicity.</p>
		<p>Sponsor Comment:</p>	<p>The sponsor needs to clarify the decision with the PBAC.</p>

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<p>DAPAGLIFLOZIN, tablet, 10 mg, Forxiga®</p> <p>AstraZeneca Australia Pty Ltd</p> <p>Change to listing</p> <p>(Minor submission)</p>	Type 2 diabetes	<p>Amendments to the current restriction for dapagliflozin for use in diabetes mellitus type 2 to provide prescribers with clarity regarding the eligible PBS population.</p>	<p>The PBAC rejected the requested restriction changes of dapagliflozin.</p> <p>The PBAC noted the sponsors claim that the word 'condition' in the current restrictions can be referred to as type 2 diabetes in its entirety, or, to the level of blood glucose, and that the interpretation of the word 'control' is also directly related to the interpretation of the word 'condition'.</p> <p>The PBAC noted that the listings data system used by the Department to give effect to PBS listings requires use of defined prefixes for clinical, treatment and population criteria used in PBS restrictions. Therefore, the PBAC considered that with the current data system, it is not possible, to change "condition" to "disease" in the clinical criteria as requested by the sponsor.</p> <p>The PBAC clarified that the term condition in the clinical criteria refers to type 2 diabetes mellitus.</p>
		Sponsor Comment:	The sponsor had no comment.
<p>DASATINIB, tablets, 20 mg, 50 mg, 70 mg, 100 mg Sprycel®</p> <p>Bristol Myers Squibb Australia Pty Ltd</p> <p>Change to listing</p> <p>(Minor submission)</p>	Chronic myeloid leukaemia	<p>The submission sought provision for second and subsequent dasatinib Authority required applications to be made via telephone (as opposed to current written-only applications), consistent with imatinib.</p>	<p>It was the PBAC's view that the existing written-only Authority approval arrangements for second and subsequent dasatinib prescriptions are not a barrier to prescribing dasatinib. The PBAC rejected the request to amend dasatinib's restriction to allow Authority for second and subsequent continuing prescriptions to be sought via telephone or other non-written methods on the basis that drug utilisation data on patient persistence with drug therapy was not presented to support the request. However, the PBAC indicated that it would be prepared to reconsider the requested change if drug utilisation data provided by the sponsor and/or the Drug Utilisation Sub-Committee on patient persistence rates for dasatinib and imatinib indicate no discernable difference.</p>
		Sponsor comment:	The sponsor disagrees with the decision.
<p>LIXISENATIDE, 10 micrograms/0.2 mL injection, 14 unit doses (&amp;) lixisenatide 20 micrograms/0.2 mL</p>	Type 2 diabetes	<p>Authority required (Streamlined) listing for treatment of diabetes mellitus type 2 as triple combination therapy with basal insulin and either metformin or a sulphonylurea in</p>	<p>The PBAC rejected the request to list lixisenatide for use in combination with insulin on the basis that the clinical place of glucagon-like peptide-1 drugs in type 2 diabetic patients requiring insulin therapy is yet to be established and therefore the appropriate comparator is not only uptitrated insulin. The basis for the cost minimisation analysis of lixisenatide compared to uptitrated insulin was therefore not accepted. Additionally, the trial based insulin dosage regimens used in the comparison were unlikely to be to be</p>

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<p>injection, 14 unit doses, Lyxumia® Treatment Initiation Pack</p> <p>lixisenatide 20 micrograms/0.2 mL injection, 28 unit doses, Lyxumia®</p> <p>Sanofi-Aventis Australia Pty Ltd</p> <p>New listing</p> <p>(Major submission)</p>	Type 2 diabetes	<p>patients who meet certain criteria.</p>	<p>replicated in practice.</p> <p>On the basis of indirect and multi-step indirect evidence presented in the submission, the comparison of lixisenatide plus basal insulin and comparator drugs (basal-bolus regimens and premixed insulin) resulted in:</p> <ul style="list-style-type: none"> <li>An approximate 0.10% to 0.32% reduction in HbA1c over a maximum duration of exposure of 24 weeks. The submission considered that a reduction of 0.4% is clinically significant, and that lixisenatide is equivalent to the comparator drugs.</li> </ul> <p>On the basis of indirect and multi-step indirect evidence presented in the submission, for every 100 patients treated with lixisenatide plus basal insulin in comparison to the comparator drugs (basal-bolus regimens and premixed insulin):</p> <ul style="list-style-type: none"> <li>Approximately 3 to 5 additional patients might stop treatment due to side effects over a median duration of exposure of 24 weeks.</li> </ul>
		Sponsor Comment:	The sponsor will be considering its position regarding any future course of action.
<p>LIXISENATIDE, 10 micrograms/0.2 mL injection, 14 unit doses (&amp;) lixisenatide 20 micrograms/0.2 mL injection, 14 unit doses, Lyxumia® Treatment Initiation Pack</p> <p>lixisenatide 20 micrograms/0.2 mL injection, 28 unit doses, Lyxumia®</p> <p>Sanofi-Aventis Australia Pty Ltd</p> <p>New listing</p>	Type 2 diabetes	<p>To request an Authority required (Streamlined) listing for treatment of diabetes mellitus type 2 in patients who meet certain criteria as;</p> <p>(i) dual therapy in combination with metformin; and</p> <p>(ii) triple therapy in combination with metformin and a sulphonylurea.</p>	<p>The PBAC rejected the submission on the basis that lixisenatide's non-inferiority to exenatide (twice daily) had not been adequately established. Therefore the PBAC did not accept the basis of the submission's cost-minimisation analysis against exenatide.</p> <p>On the basis of direct and indirect evidence presented in the submission, the comparison of lixisenatide and exenatide resulted in:</p> <ul style="list-style-type: none"> <li>An approximate 0.17% to 0.20% smaller reduction in HbA1c over a maximum duration of follow-up of 24 week. The submission considered that a reduction of 0.4% is clinically significant and that lixisenatide is equivalent to exenatide.</li> </ul> <p>On the basis of direct evidence presented in the submission, for every 100 patients treated with lixisenatide plus metformin in comparison to exenatide plus metformin;</p> <ul style="list-style-type: none"> <li>Approximately 9 fewer patients would have nausea over a median duration of exposure of 80 weeks.</li> <li>Approximately 10 fewer patients would have symptomatic hypoglycaemia (low blood sugar level) over a median duration of exposure of 80 weeks.</li> <li>Approximately 7 additional patients would have injection site reactions over a median duration of exposure of 80 weeks.</li> </ul>
		Sponsor Comment:	The sponsor will be considering its position regarding any future course of action.



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New listing  (Major submission)			
POMALIDOMIDE, capsules, 3 mg and 4 mg, Pomalyst®  Celgene Pty Ltd  New listing  (Major submission)	Myeloma	Section 100 (Highly Specialised Drug Program) Authority required listing for treatment in combination with dexamethasone, of patients with relapsed and/or refractory multiple myeloma who have received and failed prior treatment with both lenalidomide and bortezomib.	<p>The PBAC rejected the submission requesting PBS listing of pomalidomide for multiple myeloma on the basis that cost-effectiveness had not been demonstrated. The PBAC considered that multiple myeloma remains incurable while becoming an increasingly more common disease. Noting the consumer comments in support of pomalidomide, the PBAC recognised that there may be a clinical place for the drug in patients who have failed bortezomib and lenalidomide. The PBAC identified that a major resubmission would be required to address the Committee's concerns regarding the high and uncertain ICER. The base case of the economic evaluation would need to be respecified according to the PBAC's recommendations.</p> <p>On the basis of the direct intention to treat (ITT) comparison evidence presented by the submission, the comparison of pomalidomide plus low dose dexamethasone and high dose dexamethasone resulted in:</p> <ul style="list-style-type: none"> <li>• A median 7.9 weeks improvement in progression free survival and 19.1 weeks improvement in overall survival (March 2013 data cut-off).</li> <li>• Approximately 33 additional episodes of grade 3 or 4 neutropenia, 5.7 episodes of grade 3 or 4 leukopenia and an additional 9.3 episodes of grade 3 or 4 febrile neutropenia over an average treatment duration of 5.5 months.</li> </ul>
		Sponsor Comment:	The sponsor needs to clarify the decision with the PBAC.
REGORAFENIB, tablet, 40 mg, Stivarga®  Bayer Australia Ltd  New listing  (Major submission)	Metastatic colorectal cancer (mCRC)	Authority required (Streamlined) listing for treatment of patients with metastatic colorectal cancer (mCRC) who have a WHO performance status of 0 or 1, following failure of or intolerance to prior therapy.	<p>The PBAC rejected the submission on the basis that the observed improvement in comparative effectiveness associated with regorafenib was small and of uncertain clinical significance especially in the context of the increase in serious adverse effects associated with treatment. The most reliable estimate of the incremental cost-effectiveness ratio for regorafenib compared to best supportive care, presented in the model and as revised by the ESC, remains unacceptably high, particularly given the small incremental benefit observed in the trials.</p> <p>The PBAC noted on the basis of direct comparison of regorafenib with best supportive care (BSC):</p> <ul style="list-style-type: none"> <li>• the improvement in median progression-free survival was approximately 6 days,</li> </ul>

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			<p>and the improvement in median overall survival was approximately 43 days.</p> <ul style="list-style-type: none"> <li>for every 100 patients treated with regorafenib compared with BSC: <ul style="list-style-type: none"> <li>1 patient would die from a treatment-related adverse event.</li> <li>16 patients would experience hand/foot adverse events.</li> <li>6 patients would experience diarrhoea.</li> </ul> </li> </ul>
		Sponsor Comment:	The sponsor had no comment.
<p>SOFOSBUVIR. tablet, 400 mg, Sovaldi®</p> <p>Gilead Sciences Pty Ltd</p> <p>New listing</p> <p>(Major submission)</p>	Hepatitis C	<p>Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required (Streamlined) listing for the treatment of genotypes 1, 2, 3, 4, 5, and 6 hepatitis C viral infection in patients 18 years or older who have compensated liver disease.</p>	<p>The PBAC rejected the submission for Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing for sofosbuvir for the treatment of chronic hepatitis C on the basis of unacceptably high and likely underestimated cost-effectiveness and the high and likely underestimated budgetary impact on the PBS.</p> <p>The PBAC recognised that treatment of hepatitis C virus (HCV) can be curative, compared to other viral infections such as human immunodeficiency virus (HIV) and hepatitis B virus, and that sofosbuvir is the first oral direct acting antiviral agent (DAA) which can be used to treat HCV genotypes 1-6 and to provide patients with the first interferon-free treatment option. The PBAC considered that consideration of new treatment options for HCV should be framed in the evolving treatment landscape where patients are most likely waiting for the availability of interferon-free regimens.</p> <p>The PBAC noted that HCV Genotype 1 or Genotype 3 account for 88-92% of infections in Australia. The PBAC considered that the ICER/QALYs were high and uncertain in IFN-free regimes for treatment for genotype 1 and genotype 3 compared to no treatment, which the PBAC considered to be the most informative treatment groups for decision making in the broader context of HCV treatment.</p> <p>The financial estimates presented in the submission estimated that listing sofosbuvir would have a high financial impact on the health budget. The PBAC considered that the estimates were likely underestimated due to increasing number of patients seeking treatment regimens which are of shorter duration, less adverse effects and are interferon-free.</p> <p>The PBAC considered, as the clinical management of individuals with HCV is moving so rapidly, that a broader Government and community approach is needed to maximise clinical outcomes and patient access to treatment. As well as subsidising new treatment on the PBS, other factors that increase the capacity to treat patients need to</p>

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			<p>be explored.</p> <p>Independent of the submission, the Transplantation Society of Australia and New Zealand (TSANZ) and the Australian Liver Association (ALA) corresponded with the PBAC, highlighting patients with a high clinical need for treatment, namely patients with HCV infection who are awaiting a liver transplant or have cirrhosis complicated by severe portal hypertension. Through clinical evidence is emerging of the benefit to these patient populations with treatment with interferon-free regimens, the comparative clinical benefit had not been presented to the committee and cost-effectiveness had not been established. The PBAC considered that establishing cost-effectiveness in this high need population may be an early step towards a broader access for a treatment for Australians with HCV infection.</p>
		Sponsor Comment:	The sponsor needs to clarify the decision with the PBAC.
<p>SORAFENIB, tablet, 200 mg, Nexavar®</p> <p>Bayer Australia Ltd</p> <p>Change to listing</p> <p>(Major submission)</p>	Thyroid Cancer	<p>Authority required listing for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.</p>	<p>The PBAC rejected the submission for PBS listing of sorafenib for differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI-R) on the basis of high and uncertain cost effectiveness, a sub-optimally defined patient population and uncertain clinical benefit.</p> <p>The PBAC considered that there may be a small population for which this drug may be of benefit - in patients with rapid disease and symptomatic progression where the prognosis is poorer. However the submission did not provide sufficient data to define this group of patients and how they would be identified in clinical practice. The PBAC considered that it was uncertain whether a gain in progression free survival (PFS) was clinically meaningful in this type of cancer, in the absence of evidence of a benefit in overall survival (OS), noting that before progression, health related quality of life data from the trial favoured placebo compared with sorafenib. The PBAC considered that due to the sub-optimally defined nature of the treatment population, and insufficient evidence to support a meaningful clinical benefit, the resulting incremental cost-effectiveness ratio is high and uncertain. The PBAC considered that a major resubmission would be required to address the Committee's concerns, with particular regard to defining the eligible treatment population and providing evidence of a meaningful clinical benefit with sorafenib in the treatment of radioactive iodine-refractory differentiated thyroid cancer.</p> <p>On the basis of the direct evidence presented by the submission, the comparison of sorafenib with placebo resulted in:</p>

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			<ul style="list-style-type: none"> <li>a significant increase in median PFS compared with placebo from 5.8 months (placebo) to 10.8 months (sorafenib). Censoring of patients who ceased sorafenib early due to side effects without progression may bias this result towards sorafenib;</li> <li>a significant increase in 'Disease Control', which comprises complete response, partial response and stable disease. The disease control rate was 74.6% in the placebo arm compared with 86.2% in the sorafenib arm.</li> </ul> <p>On the basis of the direct evidence presented by the submission, the comparison of sorafenib with placebo did not result in a statistically significant difference in OS for the intention to treat population.</p> <p>On the basis of the direct evidence presented in the submission, for every 100 patients treated with sorafenib in comparison with placebo, approximately:</p> <ul style="list-style-type: none"> <li>38 additional patients will have at least one Grade 3 or higher adverse event.</li> <li>40 additional patients will have sorafenib treatment interrupted due to an adverse event.</li> <li>15 additional patients will have sorafenib treatment stopped due to an adverse event.</li> </ul> <p>This is based on a period of 10 – 12 months of treatment with sorafenib (compared with 8 – 9 months of observation in the placebo+ best supportive care arm).</p>
		Sponsor Comment:	The sponsor had no comment.
<p>VEDOLIZUMAB, 300 mg injection, 1 x 300 mg vial, Entyvio®</p> <p>Takeda Pharmaceuticals Australia Pty Ltd</p> <p>New listing</p> <p>(Major submission)</p>	Ulcerative colitis (UC)	<p>Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required listing for treatment of moderate to severe ulcerative colitis (UC) in patients who have failed conventional therapies and who meet certain criteria.</p>	<p>The PBAC rejected the submission to list vedolizumab for the treatment of moderate to severe ulcerative colitis on the basis that the evidence presented did not conclusively establish non-inferiority of vedolizumab to infliximab in terms of comparative safety and effectiveness. Therefore a cost-minimisation listing was not able to be supported. The cost-effectiveness of listing vedolizumab compared to placebo was unacceptably high. Further, the cost-effectiveness of listing vedolizumab following treatment failure with 5-aminosalicylate therapies, oral immunosuppressive systemic therapies and an anti-TNF alfa inhibitor, was unknown.</p> <p>On the basis of direct evidence presented by the submission, for every 100 patients treated with vedolizumab in comparison to placebo at the end of the 6 week induction treatment:</p> <ul style="list-style-type: none"> <li>Approximately 22 additional patients would have clinical response;</li> <li>Approximately 12 additional patients would have clinical remission; and</li> </ul>



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			<ul style="list-style-type: none"> <li>There is potentially no difference in the number of patients experiencing any adverse event.</li> </ul> <p>On the basis of the indirect comparison evidence presented by the submission for every 100 patients treated with vedolizumab in comparison to adalimumab for a maximum duration of 52 weeks, approximately the same number of patients would have clinical remission and adverse events.</p> <p>On the basis of the indirect comparison evidence presented by the submission, for every 100 patients treated with vedolizumab in comparison to infliximab over a maximum duration of exposure of 52 weeks, approximately the same number of patients would have clinical remission and adverse events.</p>
VORTIOXETINE, tablets, 5 mg 10 mg , 15 mg and 20 mg, Brintellix®  Lundbeck Australia Pty Ltd  New listing  (Major submission)	Major depressive disorders	Authority required listing for treatment of major depression disorder in patients aged 18 years or older who have failed to respond to, or are intolerant/contraindicated to other antidepressant therapy	Sponsor Comment: The sponsor will be considering its position regarding any future course of action.
			<p>The PBAC rejected the submission on the basis that the clinical place of vortioxetine relative to Serotonin Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) was unclear and on the basis that the PBAC did not accept the claim of non-inferiority of vortioxetine compared to duloxetine. Therefore, the cost-minimisation analysis against desvenlafaxine alone and the pre-PBAC response's proposal to list vortioxetine on a cost-minimisation basis against a weighted SNRI class were not accepted. In its consideration of the relevant comparator, the PBAC was of the view that there was insufficient reason to exclude SSRIs from an economic comparison which consequently did not support a cost-minimisation analysis of vortioxetine against a weighted SNRI class of drugs.</p> <p>On the basis of direct evidence presented by the submission, the comparison of vortioxetine and venlafaxine resulted in:</p> <ul style="list-style-type: none"> <li>No statistically significant difference in change on the MADRS (Montgomery–Åsberg Depression Rating Scale scale) over the trial period (six to eight weeks). It is considered that a reduction of 1.6 to 1.9 is clinically significant.</li> </ul> <p>On the basis of direct evidence presented by the submission, the comparison of vortioxetine and duloxetine resulted in:</p> <ul style="list-style-type: none"> <li>A 2.31 increase (favouring duloxetine) in baseline change on the MADRS scale over the trial period (six to eight weeks). It is considered that a change of 1.6 to 1.9 is clinically significant.</li> </ul>

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			<p>Based on these trials and the most favourable results for vortioxetine, for every 100 patients treated with vortioxetine compared to venlafaxine:</p> <ul style="list-style-type: none"> <li>• Up to 3 fewer patients would experience a serious adverse event (based on Trial 13926A);</li> <li>• Up to 9 fewer patients would experience an adverse event leading to withdrawal from treatment (based on Trial 11492A).</li> </ul> <p>Based on these trials and the most favourable results for vortioxetine, for every 100 patients treated with vortioxetine compared to duloxetine:</p> <ul style="list-style-type: none"> <li>• Up to 2 less patients would experience a serious adverse event (based on Trial 13267A);</li> <li>• Up to 4 less patients would experience an adverse event leading to withdrawal from treatment (based on Trial 12541A).</li> </ul>
		Sponsor Comment:	The sponsor disagrees with the decision and will be considering its position regarding any future course of action.