MARCH 2017 PBAC OUTCOMES – 1ST TIME DECISIONS NOT TO RECOMMEND

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ADALIMUMAB Injection 40 mg in 0.8 mL pre-filled syringe Injection 40 mg in 0.8 mL pre-filled pen Humira® AbbVie Pty Ltd Change to Listing (Major Submission)	Non-infectious intermediate, posterior or panuveitis uveitis (inflammatory disease of the eye)	To request an Authority Required listing for the treatment of vision threatening non-infectious intermediate, posterior or panuveitis uveitis.	The PBAC did not recommend the listing of adalimumab for the treatment of non-infectious intermediate, posterior uveitis or panuveitis due to low confidence in the size of the effect compared with current treatment and uncertain cost effectiveness compared to placebo. The PBAC considered that the clinical trials presented in the submission did not accurately reflect the context of the use being proposed, treatment for patients who have not achieved adequate response to corticosteroid therapy and immunomodulatory therapy. Furthermore, the clinical relevance of measures used to define uveitic flares and its relationship to the development of ocular complications was not clearly defined so conclusions about adalimumab's clinical impact could not be made. On the basis of the direct evidence from the VISUAL I trial presented in the submission, treatment with adalimumab compared with placebo resulted in a median of 2.6 months longer time to treatment failure (worsening of inflammatory markers in the eye or of visual acuity) for patients with active inflammatory disease at baseline. On the basis of the direct evidence from the VISUAL II trial treatment with adalimumab compared with placebo resulted in a statistically significantly longer time to treatment failure (worsening of inflammatory markers in the eye or of visual acuity) for patients with controlled disease requiring relatively high doses of oral corticosteroids to maintain remission. 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. The PBAC acknowledged there was high clinical need for additional effective treatment options for patients who have not achieved adequate response to corticosteroid therapy and immunomodulatory therapy.

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		Sponsor Comment:	AbbVie welcomes the PBAC's acknowledgement of the unmet clinical need for an effective treatment for patients with non-infectious intermediate, posterior or pan-uveitis, however is disappointed in the PBAC's decision to reject the adalimumab submission for this condition. Abbvie will consider how it is able to respond to the queries raised by the PBAC.
EMPAGLIFLOZIN WITH LINAGLIPTIN Tablet containing 10 mg empagliflozin with 5 mg linagliptin Tablet containing 25 mg empagliflozin with 5 mg linagliptin Glyxambi® Boehringer Ingelheim Pty Ltd New Listing (Major Submission)	Type 2 diabetes	To request an Authority Required (STREAMLINED) listing for use as add-on therapy to metformin for the treatment of diabetes mellitus type 2.	The PBAC did not recommend listing empagliflozin (25 mg or 10 mg) + linagliptin 5 mg fixed dose combination tablet (FDC) in combination with metformin for treatment of type 2 diabetes mellitus (T2DM) on the PBS. The PBAC judges the merit of funding drugs on the basis of comparative effectiveness and cost-effectiveness to current funded treatments. Patients with diabetes mellitus type 2 can currently access a number of different treatments. Overall, the submission did not provide convincing data that empagliflozin (25 mg or 10 mg) + linagliptin 5 mg FDC was sufficiently as effective or as cost-effective as the current funded treatments nominated in the submission, so the PBAC was unable to judge the merit of the submission's proposed listing. In addition, the PBAC considered that the requested restriction would not be implementable in practice and the clinical need and place in therapy were not well defined.
		Sponsor Comment:	The sponsor had no comment.
PALBOCICLIB Capsule 75 mg Capsule 100 mg Capsule 125 mg Ibrance® Pfizer Australia Pty Ltd	Hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer	To request an Authority Required listing with a non-steroidal aromatase inhibitor (letrozole or anastrozole) as initial endocrine-based therapy in postmenopausal women with hormone receptor positive, HER2 negative advanced breast cancer.	The PBAC did not recommend the listing of palbociclib on the PBS as initial endocrine-based therapy for hormone receptor positive (HR+), HER2-negative (HER2–) advanced breast cancer on the basis that: • the PBAC did not know the circumstances that palbociclib would be registered for use in Australia • there is strong clinical benefit of endocrine-based therapy alone as first-line therapy in many patients, and uncertainty as to which patients would most benefit from the addition of palbociclib • a number of effective and well-tolerated second-line therapies

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			(including oral treatments) are available for patients who progress after first-line endocrine-based therapy • palbociclib is associated with significant toxicity • the effect of palbociclib on overall survival is uncertain • palbociclib is associated with high and uncertain cost-effectiveness • the likely net cost of listing palbociclib to the PBS would be $50-$75 million in the first year and more than $100 million per year in the subsequent four years, and as such, there would be a significant opportunity cost to the Commonwealth. The PBAC noted that breast cancer is the most common cancer in females and that the majority of patients with advanced breast cancer patients have the HR+ / HER2 negative type (approximately 70% based on DUSC advice). The PBAC welcomed the comments received via the Consumer Comments facility on the PBS website. The PBAC considered that the clinical benefit of adding palbociclib to letrozole was uncertain because although the results of the clinical trials (called PALOMA-1 and PALOMA-2) presented in the submission showed a progression-free survival (PFS) benefit associated with the use of palbociclib (that is delaying the cancer getting growing again and the next treatment choice), there were no improvements in overall survival nor any improvement in patient's quality of life. In addition, the PBAC noted that many women with advanced breast cancer are managed effectively on hormone therapy only, and the next line chemotherapies include well-tolerated oral therapies. Therefore the benefit of palbociclib in delaying time to chemotherapy is uncertain, particularly given that palbociclib itself is associated with significant toxicities. The PBAC noted that there appears to be significant toxicity associated with the use of palbociclib, as patients who received palbociclib in the trials reported increased numbers of adverse events compared to those treated with letrozole alone, and that this was particularly important for a therapy that may be taken for a prolonged period.

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			On the basis of direct evidence presented by the submission, there would be approximately a 10 month increase in median PFS in patients treated with palbociclib plus letrozole in comparison with letrozole alone. A statistically significant increase in overall survival was not demonstrated in the clinical trials, nor an improvement in quality of life. For every 100 patients treated with palbociclib plus letrozole in comparison with letrozole alone, over a median follow-up with patients of around 23 months: • Approximately 54 additional patients would experience a grade ≥3 adverse event; • Approximately 74 additional patients would experience neutropenia; • Approximately 2 additional patients would experience febrile neutropenia; • Approximately 38 additional patients would experience leukopenia: • Approximately 12 additional patients would experience fatigue; and • The risk of pulmonary embolism is small but consistent in both clinical trials. The PBAC was concerned, notwithstanding the on-going TGA evaluation at the time of the PBAC's consideration, that the submission's currently reported efficacy (with no demonstrated improvement in overall survival) and harms, and the risk that a large number of patients would be exposed to important adverse events who may have obtained strong clinical benefit from endocrine-based therapy alone as first-line therapy, indicated that the sponsor had not yet identified the patient population who would get most benefit nor justified the approach to estimating the cost-effectiveness of this treatment on the PBS, at the price proposed by the sponsor. The PBAC considered the economic model in the submission and the sponsor's responses to be unreliable for decision making. The PBAC considered that increased cost to the health care system for the potential patient benefit of palbociclib over the treatments currently available in Australia would be substantially greater than the sponsor claimed, and

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			would have an opportunity cost by limiting the ability of the PBS to fund other therapies for cancer and other conditions.
		Sponsor Comment:	The Sponsor is committed to working with the PBAC and the Department of Health to make palbociclib available for the treatment of locally advanced and metastatic HR-positive, HER2-negative breast cancer.
PEMBROLIZUMAB Injection concentrate for I.V. infusion 100 mg in 4 mL Powder for injection 50 mg Keytruda® Merck Sharp and Dohme (Australia) Change to listing (Major Submission)	Non-small cell lung cancer	To request a listing under Section 100 (Efficient Funding of Chemotherapy) as first line monotherapy in patients expressing PD-L1 for non-small cell lung cancer.	The PBAC decided not to recommend that pembrolizumab be listed in the PBS for the first line treatment of programmed death ligand 1 (PD-L1) positive non-small cell lung cancer (NSCLC) on the basis of unfavourable and uncertain cost-effectiveness. The PBAC recognised that there is a clinical need for new treatments for patients with NSCLC, and that there is a clinical place for pembrolizumab in this population. As with the previous submission for second- and third-line pembrolizumab treatment for NSCLC, the PBAC also considered that the use of the proposed biomarker (≥50% tumour proportion score (TPS) threshold from PD-L1 testing) to define an optimal patient population most likely to respond to first-line pembrolizumab treatment was not adequately justified. The PBAC considered that advice from the Medical Services Advisory Committee (MSAC) would be informative on whether identifying the eligible population for PBS subsidy on the basis of the expression of PD-L1 was appropriate. On the basis of the direct evidence presented in the submission for untreated NSCLC Stage IV patients given treatment with pembrolizumab instead of first-line platinum-based chemotherapy for a median duration of 11 months: • There was a statistically significant overall survival benefit associated with pembrolizumab over chemotherapy, but the data remain immature as the difference in median overall survival is

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			unknown. The risk of death over 11 months was reduced by almost 40%. There was also a statistically significant increase in progression-free survival (difference in medians of approximately 4 and a half months); • For every 100 patients, 27 fewer patients would experience a drug-related Grade 3–5 AE, but an additional 9 patients may experience a Grade 3, 4 or 5 immune mediated AE. The risk of these immune-mediated events may be higher in clinical practice than that observed during the trial. This conclusion applies to patients with tumours which do not have an activating Epidermal Growth Factor Receptor (EGFR) gene mutation or Anaplastic lymphoma kinase (ALK) gene rearrangement, but have high expression levels of PD-L1 (TPS ≥50%). The PBAC concluded that pembrolizumab was more effective than its main comparator, platinum-based doublet chemotherapy, in NSCLC which is PD-L1 positive (TPS ≥50%), but that the magnitude of the gain in overall survival was less clear due to the observed follow-up being less than one third that of the modelled extrapolation in the economic analysis. The PBAC considered that pembrolizumab would likely be better tolerated overall than platinum-based doublet chemotherapy, however, was more likely to increase the risk of immune-related adverse events. The PBAC advised that, with the high medicine cost at the requested price, incremental cost-effectiveness of pembrolizumab was unfavourable and uncertain. The PBAC considered that MSAC advice would be informative in relation to this economic evaluation. The rationale is that the test helps exclude patients who benefit less from treatment with pembrolizumab. In the context of concerns that testing of patients for PD-L1 expression in regular practice is unlikely to identify similarly eligible patients as were identified in the evidence provided to the PBAC, the clinical benefit of the medicine may be reduced, and thus its cost-effectiveness may become even less favourable.

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			The PBAC noted that the estimated overall net cost of PD-L1 testing and pembrolizumab for NSCLC to the Government would be substantial, and as such, there would be a significant opportunity cost to the Commonwealth.
		Sponsor Comment:	The sponsor is disappointed with this outcome and will continue to work with government to bring KEYTRUDA to 1st line non-small cell lung cancer patients as soon as possible.
POMALIDOMIDE Capsule 3 mg Capsule 4 mg Pomalyst® Celgene Pty Ltd Change to listing (Minor Submission)	Relapsed/refractory multiple myeloma (RRMM)	To request an amendment to the Section 100 (Highly Specialised Drugs) listing to include patients with relapsed or refractory multiple myeloma who have received treatment with both lenalidomide and bortezomib and have experienced severe intolerance or toxicity unresponsive to adjusted dose or scheduling of lenalidomide and/or bortezomib.	The PBAC rejected the request to amend the current restriction for pomalidomide to include the treatment of patients who have experienced severe intolerance or toxicity to lenalidomide and/or bortezomib for relapsed/refractory multiple myeloma. In making its decision, the PBAC noted that cost-effectiveness in the extended population had not been demonstrated. Further, the PBAC noted that no safety data was provided to support the use of pomalidomide in patients with severe intolerance to lenalidomide.
		Sponsor Comment:	Whilst disappointed with the views expressed by the PBAC Celgene will continue to try and address the issues raised.

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RANOLAZINE Tablet (modified release) 375 mg Tablet (modified release) 500 mg Tablet (modified release) 750 mg Ranexa® A. Menarini Australia Pty Ltd New Listing (Major Submission)	Stable angina pectoris	To request an Authority Required (STREAMLINED) listing as an add-on therapy for the symptomatic treatment of stable angina pectoris.	The PBAC did not recommend the listing of ranolazine for add-on symptomatic treatment of stable angina pectoris in patients with inadequate symptom control despite taking the maximum tolerated dose of a beta-blocker or a calcium channel blocker on the basis that the nominated comparator (treatments likely to be replaced in practice) was not appropriate, the magnitude of any clinical benefit remained unclear and cost-effectiveness was uncertain. The PBAC judge the merit of funding drugs on the basis of the comparative effectiveness and cost-effectiveness to current funded treatments. Patients with stable angina pectoris can currently access long acting nitrates, nicorandil and perhexiline. Overall, the submission did not provide convincing data that ranolazine was sufficiently more effective or cost-effective than the current funded treatment of nicorandil and perhexiline. The submission did not consider long acting nitrates as a comparator. Therefore, the PBAC was unable to judge the merit of the submission's proposed listing. The PBAC considered that the clinical trials presented in the submission did not accurately reflect the proposed PBS population or current clinical practice. Furthermore, the PBAC was unsure of the clinical relevance of the difference in exercise treadmill test duration when treated with ranolazine, which was used as the main outcome of the clinical trial. There were concerns that the assumptions used in the economic analysis did not reflect current clinical practice, such as not including long acting nitrates as a comparator in the model. The PBAC considered that the incremental cost effectiveness ratio presented in the submission's base case analysis was highly uncertain.
		Sponsor Comment:	Menarini will continue to work with the PBAC as we believe there are patients in Australia who could benefit from this treatment.

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TOLVAPTAN Tablet 15 mg Tablet 30 mg Pack containing 28 tablets 15 mg and 28 tablets 45 mg Pack containing 28 tablets 30 mg and 28 tablets 60 mg Pack containing 28 tablets 30 mg and 28 tablets 90 mg Jinarc® Otsuka Australia Pharmaceutical Pty Ltd New Listing (Major Submission)	Autosomal dominant polycystic kidney disease	To request an Authority Required listing for the treatment of autosomal dominant polycystic kidney disease.	The PBAC decided not to recommend the listing of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD). The PBAC judges the merit of funding drugs on the basis of comparative effectiveness and cost-effectiveness to current funded treatments, in this case, best supportive care. The PBAC was uncertain about the long-term clinical benefit of tolvaptan in the treatment of ADPKD and that it was concerned about the substantial liver toxicity associated with the use of this drug. Overall, the submission did not provide convincing data that tolvaptan was sufficiently more effective or cost-effective than the best supportive care, so the PBAC was unable to judge the merit of the submission's proposed listing.
		Sponsor Comment:	While disappointed by the decision, Otsuka Australia Pharmaceutical is committed to providing additional evidence and work with the PBAC to ensure tolvaptan is PBS listed and available to patients with ADPKD as soon as possible.