JULY 2018 PBAC OUTCOMES – 1ST 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 OUTCOME
BLINATUMOMAB Powder for I.V. infusion 38.5 micrograms Blincyto® Amgen Australia Pty Ltd Change to listing (Major Submission)	Acute lymphoblastic leukaemia (ALL)	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of B-Cell precursor ALL in patients in haematological complete remission with minimal residual disease following induction chemotherapy.	The PBAC did not recommend the proposed Section 100 Authority Required (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD). This decision was due to the patient population in the Australian setting not being well defined, the difficulty in estimating the incremental benefit and comparative safety versus standard of care chemotherapy, and the high and uncertain incremental cost-effectiveness ratio. The PBAC considered that there is a high clinical need for more effective treatments for B-ALL, particularly in the first-line setting where there may be the greatest potential for impact on cure rates. The PBAC considered that blinatumomab is effective in eliminating MRD, but considered that the magnitude of any improvement in overall survival could not be determined from the data presented due to the immaturity of the BLAST study data, and the result of the study being confounded by stem cell transplant, In addition, there were concerns with the limitations and lack of applicability of the indirect comparison methods used in the submission, and the lack of statistically significant overall survival gain reported in the more reliable of the two comparison methods provided. The PBAC noted that no comparative adverse event data were provided for the MRD population. The PBAC considered that blinatumomab and standard of care chemotherapy have different safety profiles, with both therapies being associated with potentially life-threatening complications.
		Sponsor Comment:	Amgen is pleased that the PBAC acknowledged the clinical need for effective treatment for B-ALL. The elimination of MRD with blinatumomab is an important and effective treatment option for these patients. As such, Amgen will continue to work with the PBAC with the aim to make blinatumomab available for these patients.

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BRENTUXIMAB VEDOTIN Powder for I.V. infusion 50 mg Adcetris® Takeda Pharmaceuticals Australia Pty Ltd Change to recommended listing (Major Submission)	Refractory or relapsed CD30 positive cutaneous T-cell lymphomas (CTCL)	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of refractory or relapsed CD30 positive cutaneous T-cell lymphomas (CTCL).	The PBAC did not recommend the listing of brentuximab vedotin in relapsed or refractory CD30 positive CTCL in patients who have previously used systemic therapy, due to major reservations regarding the clinical trial evidence comparing brentuximab vedotin and vorinostat (the submission's main comparator). This meant that cost-effectiveness against vorinostat was unable to be assessed. The PBAC also considered that brentuximab vedotin was not cost-effective compared with methotrexate (the submission's supplementary comparator) at the proposed price. The PBAC noted that the incremental cost effectiveness ratio (ICER) presented was unacceptably high, even in the context of a difficult to treat and relatively rare disease.
		Sponsor Comment:	Although disappointed, Takeda will work with the PBAC to resolve the Committee's concerns to enable as timely access as possible to brentuximab vedotin on the PBS for patients with this rare and debilitating cancer.
CERLIPONASE ALFA Solution for infusion 150 mg with flushing solution Brineura® BioMarin Pharmaceutical Australia Pty Ltd New listing (Major Submission)	Neuronal ceroid lipofuscinosis type 2 (CLN2) disease (also known as tripeptidyl peptidase 1 deficiency)	To request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease.	The PBAC did not recommend the listing of cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease. The PBAC noted that based on the evidence provided, there was a benefit of treatment in terms of slowing disease progression. However, the PBAC were uncertain of the magnitude of benefit given issues around trial design, and uncertainty whether the trial population was reflective of the Australian patient population. The PBAC also noted that the primary outcome reported in the trial of motor-language score did not account for all aspects of CLN2 disease. The PBAC considered that there was uncertainty whether treatment is associated with a survival benefit. The PBAC considered the incremental cost effectiveness ratio (ICER) presented in the submission's base case analysis to be unacceptably high (>$200,000 per quality adjusted life year gained) and very uncertain.
		Sponsor Comment:	BioMarin looks forward to working with the Life Saving Drugs Program to bring this important treatment to CLN2 patients in Australia.

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DENOSUMAB Injection 120 mg in 1.7 mL Xgeva® Amgen Australia Pty Ltd Change to listing (Major Submission)	Multiple myeloma (MM)	To request an Authority Required (STREAMLINED) listing for the treatment of multiple myeloma.	The PBAC did not recommend extending the current Streamlined Authority Required listing for denosumab to include treatment of patients with multiple myeloma. Although the clinical evidence indicated non-inferiority to zoledronic acid for the outcome of skeletal-related events (SREs), the PBAC considered there was an inadequate basis for accepting the claim of superior effectiveness compared to zoledronic acid and the incremental cost-effectiveness based on superior progression-free survival was implausible. The PBAC noted that the sponsor indicated they would not pursue listing if denosumab were recommended on a cost-minimisation basis with the comparator, zoledronic acid.
		Sponsor Comment:	Amgen is committed to working with the PBAC towards the listing of denosumab in multiple myeloma where there is a clinical need for an alternative to bisphosphonate therapy.
DUPILUMAB Injection 300 mg in 2 mL single dose pre-filled syringe Dupixent® Sanofi-aventis Australia Pty Ltd New listing (Major Submission)	Severe atopic dermatitis	To request an Authority Required listing for the treatment of patients with severe atopic dermatitis who have had an inadequate response, intolerance or contraindication to treatment with cyclosporin.	The PBAC did not recommend the listing of dupilumab for the treatment of severe atopic dermatitis due to uncertainty regarding the appropriate place in therapy and uncertain cost effectiveness. The PBAC did not consider that the data presented in the submission supported restricting use of dupilumab only to severe disease. The PBAC acknowledged the clinical need for a safe and effective treatment for patients with atopic dermatitis who do not respond to existing therapies.
		Sponsor Comment:	Sanofi welcomes the Committee's recognition of the need for a safe and effective treatment for patients with atopic dermatitis and remains committed to working with the PBAC to enable reimbursed access to dupilumab for Australian patients with atopic dermatitis unresponsive to existing therapies.

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ERENUMAB Injection 70 mg in 1 mL single dose pre-filled pen Aimovig® Novartis Pharmaceuticals Australia Pty Ltd New listing (Major Submission)	Chronic migraine	To request an Authority Required (STREAMLINED) listing for prophylaxis in patients with chronic migraine.	The PBAC did not recommend the Authority Required (Streamlined) listing of erenumab for the treatment of chronic migraine. The PBAC considered that the submission had neither adequately justified the place in therapy nor justified the proposed PBS listing, which excluded migraine patients that may benefit from this treatment. The evidence used for the basis of the clinical claim that erenumab was more effective than botulinum toxin had significant limitations, resulting in a clinical effectiveness and cost-effectiveness estimates that were highly unreliable for decision making. In addition, the PBAC considered that the cost to Government was underestimated by the submission, both because the number of patients with chronic migraine was underestimated by the submission and because of the significant risk of leakage outside the proposed limited PBS listing (for example, patients with episodic migraine). The PBAC acknowledged the unmet clinical need for new treatments (including erenumab) for sufferers of migraine, and looks forward to engaging with the company to find a way forward.
		Sponsor comment	Novartis remains committed to working with the PBAC to enable reimbursed access to erenumab for Australian patients with migraine.

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LETERMOVIR Tablet 240 mg Prevymis® Merck Sharp & Dohme (Australia) Pty Ltd New listing (Major Submission)	Prophylaxis of cytomegalovirus (CMV) infection or disease	To request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive [R+] recipients of an allogeneic haematopoietic stem cell transplant (allo-HSCT).	The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing for letermovir for prophylaxis of cytomegalovirus (CMV) infection or disease in CMV sero-positive patients who have received an allogeneic haematopoietic stem cell transplant (HSCT). This decision was on the basis that the Committee was unable to assess the cost-effectiveness of letermovir treatment because the economic analysis did not appropriately model the health benefits of treatment as demonstrated in the clinical trial. The PBAC noted the consumer comments and acknowledged the clinical utility of an orally active agent to prevent CMV infection and that letermovir was less toxic than currently used antiviral treatments. The PBAC noted that antiviral treatments are used in Australian practice, either prophylactically (preventative treatment) or as pre-emptive therapy (PET, treatment after detection of CMV), and their use would likely reduced with the availability of letermovir. The PBAC considered that, in addition to placebo (the submission's comparator), other antiviral treatments would be an informative comparator. The PBAC considered that letermovir treatment reduces the use of PET, but that a difference in CMV disease and associated sequalae, including graft vs host disease (GVHD) and all-cause mortality, had not been demonstrated. The PBAC considered that the economic model should be based on the health benefits as demonstrated in the trial rather than trial outcomes for which there was little or no difference between the letermovir and placebo treatment groups.
		Sponsor Comment:	The sponsor is disappointed with the PBAC outcome and is committed to working with the government to ensure PREVYMIS is made available as soon as possible to all patients undergoing allogeneic bone marrow transplants who are at risk of CMV reactivation and its associated poor outcomes.

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NIVOLUMAB Injection concentrate for I.V. infusion 40 mg in 4 mL Injection concentrate for I.V. infusion 100 mg in 10 mL Opdivo® Bristol-Myers Squibb Australia Pty Ltd Change to listing (Major submission)	Malignant melanoma	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the adjuvant treatment of patients who have had completely surgically resected Stage III or Stage IV malignant melanoma.	The PBAC did not recommend nivolumab for use in patients with resected Stage III and Stage IV melanoma. The PBAC acknowledged that there was a high unmet clinical need for effective therapies to reduce the risk of recurrence of resected stage III and IV melanoma, and considered that in some circumstances recurrence was less likely for patients treated with nivolumab compared to placebo. However, the PBAC considered that the data presented in the submission were immature and the effect on overall survival could not be determined. As a result, the incremental cost-effectiveness ratio was highly uncertain, particularly in the context of the high opportunity cost based on the submission's estimated expenditure.
		Sponsor Comment:	The Sponsor looks forward to continuing to work with the Government to provide access to this treatment option.

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NIVOLUMAB and IPILIMUMAB nivolumab: Injection concentrate for I.V. infusion 40 mg in 4 mL Injection concentrate for I.V. infusion 100 mg in 10 mL ipilimumab: Injection concentrate for I.V. infusion 50 mg in 10 mL Injection concentrate for I.V. infusion 200 mg in 40 mL Opdivo® and Yervoy® Bristol-Myers Squibb Australia Pty Ltd New listing (Major Submission)	Renal cell carcinoma (RCC)	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STEAMLINED) listing for the concurrent use of nivolumab and ipilimumab for the treatment of Stage IV clear cell variant renal cell carcinoma (RCC).	The PBAC did not recommend nivolumab in combination with ipilimumab (NIVO+IPI) for the first-line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients at intermediate to poor prognostic risk. The PBAC acknowledged the high clinical need for effective first-line therapies, especially in patients who are categorised as being at poor prognostic risk. However, the PBAC considered that the incremental survival and quality of life benefits were overestimated in the economic model presented in the submission, and that the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The PBAC considered that a price reduction would be required to bring the estimated ICER into an acceptable range. The PBAC noted that NIVO+IPI was associated with a slight improvement in overall survival at 18 months versus sunitinib. However, the PBAC considered that the magnitude of the long-term treatment effect was uncertain and likely overestimated because the trial data were immature and the trial population may have been healthier than the likely PBS population. The PBAC considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib, because NIVO+IPI was associated with a higher rate of serious adverse events and adverse events resulting in treatment discontinuation.
		Sponsor Comment:	The Sponsor looks forward to continuing to work with the Government to provide access to this treatment option.
PEMBROLIZUMAB Solution concentrate for I.V. infusion 100 mg in 4 mL Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd	Squamous cell carcinoma for the head and neck (SCCHN)	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of patients with recurrent or metastatic SCCHN who progress on or after platinum-based chemotherapy.	The PBAC did not recommend pembrolizumab for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) squamous cell carcinoma of the head and neck who have failed a platinum-containing regimen. The PBAC considered that the clinical need was low due to the availability of alternative treatments on the PBS and that the magnitude of clinical benefit was uncertain. In addition, the PBAC considered that the clinical evidence provided did not adequately support the claim of non-inferior efficacy to nivolumab, the nominated comparator. As such, the PBAC considered that the cost minimisation analysis presented was not informative to the Committee.

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Change to listing (Major Submission)		Sponsor Comment:	The sponsor is disappointed in this PBAC outcome but will work towards obtaining funded treatment options for patients with squamous cell carcinoma of the head and neck at the earliest opportunity.
PERTUZUMAB Solution for I.V. infusion 420 mg in 14 mL Perjeta® Roche Products Pty Ltd New listing (Major Submission)	Human epidermal growth factor receptor-2 positive (HER2+) early breast cancer (EBC)	To request a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the adjuvant treatment of HER2 +, lymph node positive early breast cancer (EBC).	The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy), Authority Required listing of pertuzumab in combination with trastuzumab for the adjuvant treatment of patients with human epidermal growth factor 2 (HER2) positive early breast cancer (eBC) at high risk of disease recurrence. The submission defined patients at high risk as patients with involvement of one or more positive lymph nodes. Analysis of this population in the head to head trial called APHINITY showed a small benefit in patients treated with pertuzumab in combination with trastuzumab and chemotherapy, compared to treatment with trastuzumab in combination with chemotherapy. The PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of adverse reactions (in particular the cardiac risks and significant difference in the incidence of diarrhoea). In addition the PBAC noted that the largest population of patients with lymph node positive disease are patients who are also hormone receptor positive, and that from the trial evidence presented the clinical benefit in this patient population was uncertain. The PBAC noted changes in clinical guidelines and new trial evidence suggesting the treatment landscape for this patient population with HER2-positive early breast cancer is quickly evolving, and considered it difficult to determine the clinical place of pertuzumab in combination with trastuzumab and chemotherapy. The PBAC noted the pricing proposal in the submission and the claim of cost neutrality. However, the PBAC and its sub-committees were concerned about the claimed cost-effectiveness of this treatment and that the proposed arrangements would not provide certainty about the cost to Government over time. The PBAC's concerns regarding the sponsor's price proposal were secondary to its concerns about the modest clinical benefit of treatment with pertuzumab in combination with trastuzumab.
		Sponsor Comment:	Roche remains committed to working with the PBAC to enable access to pertuzumab for people with early breast cancer and node positive disease.

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TRIVALENT INFLUENZA VACCINE (High dose) Injection 0.5 mL Fluzone® High-Dose Sanofi-aventis Australia Pty Ltd Change to listing (Major Submission)	Prevention of seasonal influenza	To request that the PBAC review the circumstances of the recommended National Immunisation Program (NIP) listing for the prevention of seasonal influenza in patients aged 65 years and over.	Inactivated trivalent influenza vaccine (Fluzone® High-Dose, TIV-HD) is currently an influenza vaccine available on the National Immunisation Program (NIP). The PBAC did not recommend the requested change to the basis of the National Immunisation Program (NIP) listing of inactivated trivalent influenza vaccine (Fluzone® High-Dose, TIV-HD), for active immunisation against influenza in adults aged ≥65 years. This decision was made on the basis of uncertainty around the loss of protection against the alternative B lineage and the incremental benefit of the strains matched with the comparator vaccine, the associated uncertainty in assessing the incremental cost-effectiveness of the vaccine and the high financial implications of the proposed price. Given the very large opportunity cost of the proposed price change, the PBAC considered better modelling and scenario analyses around TIV-HD compared with the quadrivalent influenza vaccine standard dose (QIV-SD) using data from Australian experience over a longer time-frame was required.
		Sponsor Comment:	Sanofi is disappointed with the Committee's decision not to recommend the change to the current NIP listing for Fluzone High Dose. We will continue to work towards maintaining access to this important vaccine for Australians aged 65 years and older.