MARCH 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
ELOSULFASE ALFA 5mg/5mL injection, 5 mL vial Vimizim® Biomarin Pharmaceuticals Australia Pty Ltd New listing (Major Submission)	The treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).	Not Listed	Resubmission for Section 100 (Highly Specialised Drugs Programme) Authority Required listing for the treatment of patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome).	The PBAC did not recommend the Authority Listing Section 100 PBS listing for elosulfase alfa for the treatment of patients with mucopolysaccharidosis (MPS) IVA (Morquio A Syndrome). The PBAC considered that while there was sufficient basis to conclude that treatment with elosulfase alfa results in a small but meaningful clinical improvement, the cost effectiveness of the drug was highly uncertain and unacceptable. On the basis of direct evidence presented by the submission, a person treated with elosulfase alfa compared to placebo could expect an average improvement of 22.5 metres at 24 weeks from their baseline six minute walk test (6MWT) distance. This could be expected to improve to 45.2m at one year and 55.1m at two years. However, this improvement was heterogeneous. With respect to safety, for every 100 patients treated with elosulfase alfa in comparison to placebo for 24 weeks: • Approximately 12 additional patients will experience a serious adverse event. • Approximately 18 additional patients will experience a moderate to severe infusion associated reaction. • Approximately 19 additional patients will experience pyrexia. • Approximately 24 additional patients will experience vomiting.
			Comparator: Placebo in combination with standard medical management.	Accepted.

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			Clinical claim: elosulfase alfa as superior to placebo in terms of efficacy but associated with a slightly greater incidence of adverse events.	Accepted. The clinical evidence provided in the submission included one head-to-head trial comparing elosulfase alfa to placebo, three additional open label elosulfase alfa studies and two prospective observational studies.
			Economic claim:	Not Accepted. The PBAC did not consider the economic model was informative. The PBAC, in addition, was uncertain about a survival gain for patients treated with elosulfase alfa and the application of this gain in the economic analysis. The PBAC noted that inclusion of the resubmission's proposed pay-for-performance arrangement and financial caps in the economic analysis did not substantially reduce the incremental cost-effectiveness ratio at the price proposed by the sponsor, nor adequately contained the financial risk to the Commonwealth.
			Sponsor's comments:	BioMarin is committed to working with the PBAC and the Department of Health to make elosulfase alfa available on the PBS/LSDP for patients with MPS IVA.

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ETANERCEPT 25 mg injection [4 x 25 mg vials] (&) inert substance diluent [4 x 1 mL syringes], 1 pack; 50 mg in 1 mL single use pre-filled syringes, 4; 50 mg in 1 mL single use auto-injector, 4 Enbrel® Pfizer Australia Pty Ltd Change to listing (Major Submission)	Treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs. Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.	Severe active juvenile idiopathic arthritis Severe active rheumatoid arthritis Ankylosing spondylitis Severe psoriatic arthritis Sever chronic plaque psoriasis for adults Severe chronic plaque for patients under 18 years of age	Resubmission for Authority Required (STREAMLINED) listing for the treatment of adults with active non-radiographic axial spondyloarthritis.	The PBAC did not recommend listing of etanercept for active non-radiographic axial spondyloarthritis (nr-axSpA) on the basis of an unacceptably high and uncertain incremental cost effectiveness ratio. In addition, the PBAC considered that the patient population remained poorly defined and justified. The PBAC considered there is a clinical need for subsidised access to etanercept for this condition but noted that the clinical benefits of etanercept in nr-axSpA were modest.
			Comparator: placebo	Accepted: The PBAC recalled that it had previously accepted that placebo plus background NSAID treatment was the appropriate comparator.
			Clinical claim: Etanercept was superior in terms of efficacy and inferior in terms of safety in comparison to placebo.	Not accepted: The submission was based on a randomised controlled trial. Overall, the PBAC considered that the clinical benefits of etanercept in nr-axSpA were modest and the submission did not provide any new evidence to change the PBAC's previous conclusion that the available evidence did not enable PBAC to characterise the likely magnitude of benefit with respect to patient relevant outcomes additional to the Assessment of Spondyloarthritis International Society criteria (such as disease progression) in patients with nr-axSpA or to define a patient population with a higher treatment response. The PBAC previously considered that the claim of inferior comparative safety was reasonable.
			Economic claim: a cost-utility analysis (CUA) of etanercept versus usual care	Not Accepted. The PBAC considered that the extrapolation of a constant utility benefit associated with treatment with etanercept over 10 years was unrealistic and inappropriate, particularly in the context of a progressive disease, and given only 12 weeks of trial based data.

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				At the same time, however, the PBAC considered that a 10 year time horizon was considered too short in the context of the condition. Overall, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain.
			Sponsor's comments:	Pfizer Australia is pleased that the PBAC recognised the clinical need for subsidised treatment for nr-axSpA. However, as we lodged a re-submission aimed at resolving the issues raised previously, we are disappointed that the PBAC did not recommend listing of etanercept for nr-axSpA. This outcome means that patients with this disabling condition are still unable to access effective reimbursed treatment for their condition. As a consequence of the outcome, we are considering our options at this time.

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NINTEDANIB 100 mg capsule, 60 150 mg capsule, 60 Ofev® Boehringer Ingelhiem Pty Ltd New listing (Major Submission)	in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy	Not Listed	Re-submission for Authority Required listing for patients with locally advanced or metastatic non-small cell lung cancer.	The PBAC did not recommend the request to list nintedanib (in combination with docetaxel) for the treatment of patients with NSCLC on the basis that the resubmission did not demonstrate non-inferior effectiveness compared with pemetrexed.
			Comparator: Pemetrexed	Accepted
			Clinical claim: Non-inferior efficacy and inferior safety compared with pemetrexed monotherapy.	As in the March 2015 submission, the re-submission was based on an indirect comparison of nintedanib plus docetaxel versus pemetrexed based two head-to-head trials using docetaxel monotherapy as the common comparator. The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data. The PBAC considered that the claim of inferior comparative safety was reasonable.
			Economic claim: Cost-minimisation analysis to pemetrexed, taking into account costs of adverse events, administration and monitoring.	As in the March 2015 submission, the PBAC considered that a cost-minimisation analysis was inappropriate given that the currently available indirect evidence did not demonstrate non-inferiority for nintedanib and docetaxel compared with pemetrexed
			Sponsor's comments:	The sponsor had no comment
PIRFENIDONE 267 mg capsules, 270 Esbriet® Roche Products Pty Limited	Idiopathic Pulmonary Fibrosis	Not listed.	Re-submission to request an Authority Required listing for the treatment of idiopathic pulmonary fibrosis	The PBAC did not recommend the PBS listing of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) on the basis of unacceptably high cost-effectiveness, in the context of the total cost and remaining concerns about utilisation
			Comparator: Best Supportive Care	Accepted.

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New listing (Minor Submission)			Clinical claim: Superior in efficacy and slightly inferior in safety	Accepted.
			Economic claim: Cost-effective	Not Accepted: The PBAC considered that the most plausible incremental cost-effectiveness ratio (ICER) using the current adjustments to the model was between $45,000/QALY and $75,000/QALY. The PBAC recalled its key concerns in November 2015 regarding the derivation of the pirfenidone treated population (potentially higher IPF incidence rate; limiting calculation of prevalent population to IPF patients in the year prior to listing) and hospitalisations are likely to result in underestimated net costs to the government. The evaluation also noted additional factors (application of ABS population projections; potential duplication of deaths in the pirfenidone treatment continuation rates) that were likely to further contribute to this underestimate. The PBAC considered that the minor resubmission did not sufficiently address these issues, and noted the potential for the absence of a stopping rule to increase the utilisation estimates.
			Sponsor's comments:	Roche is disappointed with this outcome and, given the high unmet need, continues to work with the PBAC to provide access at the earliest opportunity to pirfenidone for patients with idiopathic pulmonary fibrosis.

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PRALATREXATE 20 mg/mL injection, 1 mL vial Folotyn® Mundipharma Pty Ltd New listing (Minor Submission)	Patients with peripheral T-cell lymphoma who have progressed after at least one prior therapy	Not listed.	Resubmission to request Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of patients with peripheral T-cell lymphoma.	The PBAC did not recommend the Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma (PTCL). The minor submission had not addressed the PBAC's concerns that there was insufficient evidence of the incremental clinical benefit against currently available treatments, concerns regarding a high burden of adverse events, and economic modelling was not reliable to enable the Committee to determine the cost-effectiveness of the pralatrexate in the Australian context. The PBAC considered that the incremental benefit of pralatrexate was uncertain, based on evidence from study PDX-008 (Phase 2, single-arm trial), historical control cohort from international clinical databases and a meta-analysis of fourteen single arm comparisons, provided in the original submission.
			Comparator: The basket of treatments including DHAP(high dose cytarabine, dexamethasone, cisplatin), brentuximab, gemcitabine containing regimens, methotrexate, romidepsin (not PBS listed in Australia), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), and ICE (ifosfamide, carboplatin, etoposide).	Accepted: The PBAC accepted that the basket of treatments was the appropriate main comparator. Peripheral T-cell lymphoma comprises a group of heterogeneous non-Hodgkin lymphomas that develop from T-cells in different stages of maturity.

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			Clinical claim: • Superior in terms of comparative effectiveness over single-agent and combination therapies. • In terms of comparative safety, non-inferior to single-agent therapies and superior to combination regimens.	Not Accepted: The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data. Limited data provided in the resubmission supported the claim that the toxicity of pralatrexate was consistent with other single-agent therapies, but did not adequately support the claim of superior safety in comparison with combination regimens.
			Economic claim: cost-effectiveness compared with the nominated comparator.	Not Accepted: The PBAC considered that the resubmission had not addressed the technical concerns that PBAC had with the economic model and nor the fundamental issue of the meaningfulness of this type of economic evaluation when there was insufficient clinical evidence to support the claim of superior efficacy and non-inferior safety.
			Sponsor's comments:	PTCL is a rare group of diseases. Currently, patients relapsing from, or refractory to, 1st line treatment rely on combination treatments, the evidence base for which is largely with b-cell lymphomas, not PTCL. Pralatrexate provides a valid treatment option for these patients. The Sponsor will continue working with the PBAC in order to ensure that pralatrexate is made available to patients who currently have no targeted treatment for their cancer.