MARCH 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
ABATACEPT Injection 125 mg in 1 mL single dose autoinjector Injection 125 mg in 1 mL single dose pre-filled syringe Powder for I.V. infusion 250 mg Orencia® Orencia ClickJect® Bristol-Myers Squibb Australia Pty Ltd Change to listing (Major Submission)	Psoriatic arthritis (PsA)	To request an Authority Required listing for the treatment of patients with severe active PsA.	The PBAC did not recommend abatacept for the treatment of adult patients with severe active Psoriatic Arthritis (PsA) because the availability of alternative treatments and the clinical evidence did not support the claim of non-inferior efficacy to the nominated comparators (certolizumab, ustekinumab and secukinumab).
		Sponsor Comment:	The sponsor had no comment.
ARGININE Tablet 500 mg Arginine Easy® Orpharma Pty Ltd New listing (Minor Submission)	Urea cycle disorders (UCD)	To request a Restricted Benefit listing for the treatment of UCD.	The PBAC did not recommend the listing of arginine 500 mg tablets on the basis of inappropriately high and undocumented protein content in the formulation and a lack of clinical need for an additional formulation of arginine on the PBS. The Committee noted the advice of the Nutritional Products Working Party (NPWP), which stated the levels of protein in Arginine Easy may account for up to 20% of daily protein intake in some patients, and agreed this could be detrimental to patients on highly restricted protein diets, further complicating the management of conditions which already require complex and restrictive dietary management.
		Sponsor Comment:	The sponsor recognises that a high protein content can be detrimental to patients if their diet is not properly managed, however there remains a clinical need for such dosage form as a number of centres in Australia currently provide their own tablet formulations for UCDs.

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BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX Lyophilised powder for injection 100 units Botox® Allergan Australia Pty Limited Change to recommended listing (Major Submission)	Chronic migraine	To request a revision to the existing risk sharing arrangements.	The PBAC rejected the request to revise the Risk Sharing Arrangement (RSA) relevant to the use of Botox under its PBS listing for the treatment of chronic migraine. The PBAC considered that the claim made by the submission that the RSA should be revised as the greater than predicted use of Botox was due to greater than expected efficacy, and hence was cost-effective, was not adequately supported by the evidence presented. The PBAC noted that the sponsor-funded Stark 2017 retrospective chart review served as the key evidentiary basis of the requested RSA revision, and considered that the study had a high risk of bias. The PBAC considered that, while the Stark 2017 study demonstrated higher continuation rates than the PREEMPT trial, the higher rate of continuation could potentially be attributed to other factors not directly associated with better than expected efficacy. The PBAC concluded that the evidence presented did not provide a reliable basis for a claim of greater efficacy of the use of Botox in chronic migraine than was observed in the PREEMPT trials. As the PBAC considered the submission's clinical claim was inadequately supported by the evidence provided, the committee did not accept that the approach taken to update the economic model with the results from the Stark 2017 retrospective chart review was valid. The PBAC did not accept that the data provided in the current updated model provided any greater certainty that the increased utilisation is cost effective or that the pattern of use is any more cost effective than originally anticipated. The PBAC therefore concluded there was an inadequate justification for the requested changes in the RSA structure and caps.
		Sponsor comment:	The sponsor had no comment.

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CALCIPOTRIOL with BETAMETHASONE Gel containing calcipotriol 50 micrograms with betamethasone 500 micrograms (as dipropionate) per g, 60 g Daivobet 50/500® Gel Leo Pharma Pty Ltd Change to listing (Minor Submission)	Chronic stable plaque type psoriasis vulgaris	To request additional Authority Required (STREAMLINED) listings with increased maximum quantities based on percentage of Body Surface Area (BSA) to be treated.	The PBAC did not recommend amending the listing of calcipotriol 0.005% with betamethasone dipropionate 0.05% gel, to allow access to increased quantities based on the proportion of body surface area affected by psoriasis. In making its decision, the PBAC did not consider that there was sufficient clinical need for the amendment as utilisation data indicated the majority of patients were covered by existing arrangements, and for the limited number of patients who require increased quantities of calcipotriol with betamethasone dipropionate, access is available via an Authority PBS prescription. The PBAC also considered that broader access to larger quantities may potentially increase the risk of toxicity associated with calcipotriol.
		Sponsor Comment:	The sponsor had no comment.
ECULIZUMAB Solution concentrate for I.V. infusion 300 mg in 30 mL Soliris® Alexion Pharmaceuticals Australasia Pty Limited Change to recommended listing (Minor Submission)	Atypical haemolytic uraemic syndrome (aHUS) in end stage renal disease (ESRD)	To request an extension in the recommended eculizumab treatment duration for patients with aHUS in ESRD who are eligible for a renal transplant.	The PBAC did not recommend increasing the treatment duration of PBS-subsidised eculizumab for prophylactic use in patients with end stage renal disease due to atypical haemolytic uraemic syndrome (aHUS) in the renal transplant period. The evidence presented to support the longer duration of treatment than previously recommended by the PBAC did not adequately support the proposed change and did not prove a substantial incremental benefit. As such, the PBAC re-affirmed its July 2017 recommendation that eculizumab should be available for a maximum duration of three months in this setting (ten weeks of which would be PBS-subsidised). The PBAC noted that patients with a recurrence of aHUS after this time would be eligible for eculizumab under the current listing.

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		Sponsor Comment:	Alexion is disappointed that the PBAC has not modified the previous recommendation to treat patients with aHUS undergoing renal transplant for longer than 3 months with Soliris (eculizumab). Alexion is, however, committed to ensuring that patients with aHUS who require Soliris to facilitate a renal transplant, now receive rapid access to therapy, and have the ability to access therapy again should thrombotic microangiopathy (TMA) represent in the graft. As such, Alexion look forward to working with the Department of Health and Government to ensure an expedited review of the risk sharing agreements proposed by Alexion and to ensure urgent funded access to Soliris for patients with aHUS to facilitate renal transplantation.
GUSELKUMAB Injection 100 mg in 1 mL single use pre-filled syringe Tremfya® Janssen-Cilag Pty Ltd New listing (Major Submission)	Severe chronic plaque psoriasis	To request an Authority Required listing for the treatment of severe chronic plaque psoriasis.	The PBAC did not recommend the Section 85 Authority Required listing of guselkumab for the treatment of severe chronic plaque psoriasis (CPP). In making its decision the PBAC considered that ustekinumab was an inappropriate choice as a main comparator. The PBAC considered that any of the biologic agents on the PBS for CPP may be replaced by guselkumab and hence be a relevant comparator. The PBAC agreed with ESC that infliximab was a relevant comparator, and considered that the indirect comparison presented in the Pre-PBAC response would need to be evaluated as part of a major submission. The PBAC noted the information referenced by ESC that suggested ixekizumab may be the most effective of the PBS listed biologics. Given this, the PBAC considered that a comparison versus ixekizumab would also be informative.
		Sponsor Comment:	Janssen were disappointed by this outcome, but will consider how best to address the PBAC's request in order to have Tremfya available for patients on the PBS.

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INSULIN GLARGINE WITH LIXISENATIDE Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 50 microgram per mL, 3 mL, 5 Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 33 microgram per mL, 3 mL, 5 Soliqua® Sanofi-aventis Australia Pty Ltd New listing (Major Submission)	Type 2 diabetes mellitus (T2DM)	To request an Authority Required (STREAMLINED) listing for the treatment of patients with T2DM who have inadequate glycaemic control with basal insulin.	The PBAC did not recommend insulin glargine with lixisenatide fixed ratio combination (FRC) for the treatment of patients with Type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control with basal insulin, on the basis that the equi-effective doses proposed in the submission were not accepted and hence there was no basis for determining the cost-effective price for insulin glargine with lixisenatide FRC. The submission presented an indirect comparison of two clinical trials (LIXILAN-L and GWCO). The PBAC noted differences across the trials with respect to when they were conducted, design (including that the LIXILAN-L trial had a run-in phase whereas the GWCO trial did not) and patient characteristics (including gender, ethnicity and insulin dose). The PBAC considered the claim of non-inferior comparative effectiveness to be uncertain, but may be reasonable given the key parameters which varied across the trials appear to not be treatment effect modifiers and non-inferiority was demonstrated with a 0.4% margin using the MAIC analysis. The PBAC did not accept the claimed insulin sparing effect. The PBAC considered that the claim of non-inferior comparative safety was reasonable.
		Sponsor Comment:	Sanofi will explore ways to address the issues raised by the PBAC in the hope of making Soliqua available for Australians with type II diabetes mellitus who would benefit from this product.

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LENALIDOMIDE Capsule 5 mg Capsule 10 mg Capsule 15 mg Revlimid® Celgene Pty Ltd Change to listing (Major Submission)	Multiple myeloma	To request extension to the Section 100 (Highly Specialised Drug Program) Authority Required listing to include maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone an autologous stem cell transplant.	The PBAC decided not to recommend the listing of lenalidomide for maintenance treatment of multiple myeloma following Autologous Stem Cell Transplant. The PBAC acknowledged the consumer comments received indicated a preference for lenalidomide treatment over thalidomide in the maintenance setting, particularly because of its lower rates of peripheral neuropathy. The PBAC accepted that there was evidence of improvements in progression free and overall survival compared to best-supportive care, but considered that the benefit of lenalidomide over thalidomide was not well established. For the comparison versus best-supportive care, the PBAC considered that the incremental cost-effectiveness was highly uncertain, due to concerns identified with the economic model. For the comparison versus thalidomide, the PBAC considered a cost-minimisation approach would be more appropriate than the cost-effectiveness model presented in the submission given the claim of superior efficacy for lenalidomide compared to thalidomide was inadequately supported by the evidence presented.
		Sponsor Comment:	The sponsor had no comment.
NANDROLONE DECANOATE Injection 50 mg in 1 mL ampoule Deca-Durabolin® Aspen Pharmacare Australia Pty Ltd New listing (Minor Submission)	Osteoporosis	To request an Authority Required listing of a new form of nandrolone decanoate for the treatment of osteoporosis.	The PBAC did not recommend the request of Authority Required listing of a new form of nandrolone decanoate on the basis that there was no clinical need for a new form of this drug on the PBS for the treatment of osteoporosis. In noting the lack of clinical need for nandrolone decanoate for the treatment of osteoporosis, the PBAC also agreed it had no objection to also delisting the existing PBS listed brand.
		Sponsor Comment:	The use/indication of the product was subject of evaluation during a PBAC meeting. No clinical data was submitted with the PBAC Minor submission. PBAC decided to delete a 'grandfather' indication.

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REGORAFENIB Tablet 40 mg (as monohydrate) Stivarga® Bayer Australia Ltd New listing (Major Submission)	Hepatocellular carcinoma (HCC)	To request an Authority Required (STREAMLINED) listing for the treatment of patients with unresectable HCC who have progressed on sorafenib treatment.	The PBAC did not recommend regorafenib for patients with unresectable hepatocellular carcinoma who progressed following treatment with sorafenib on the basis of a high and uncertain incremental cost-effectiveness ratio. The PBAC considered that the toxicity associated with regorafenib was substantial, with a range of adverse events associated with regorafenib, which may be more frequent and severe in the proposed Australian population compared with the trial population. The PBAC considered that the improvement in overall survival was modest, that this improvement may not be realised in clinical practice due to the trial population being younger and fitter than the proposed PBS population, and should be considered in the context of the substantial toxicity associated with regorafenib treatment. The PBAC considered that the base case ICER was underestimated due to extrapolation of the regorafenib arm only, the method of extrapolation and the use of average utilities by health state rather than trial-based utilities.
		Sponsor Comment:	Bayer remains committed to working with the PBAC to enable reimbursed access to regorafenib for Australian patients with unresectable hepatocellular carcinoma

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TIOTROPIUM Solution for oral inhalation 2.5 micrograms (as bromide monohydrate) per actuation (60 actuations) Spiriva Respimat® Boehringer Ingelheim Pty Ltd New listing (Major Submission)	Severe asthma	To request an Authority Required (STREAMLINED) listing for the treatment of severe asthma in children aged 6 years or older.	The PBAC decided not to recommend the Authority Required (STREAMLINED) listing for tiotropium solution for inhalation in patients aged 6 to 17 years old with severe asthma. The PBAC considered the claim of superior clinical effectiveness in comparison to placebo plus optimised asthma therapy to be questionable as there were several issues with the methodology and conclusions based on the clinical trials presented in the submission. The PBAC also considered the economic model based on a cost per symptomatic exacerbation avoided was problematic. The PBAC considered the primary outcome measure of the trials of Forced expiratory volume in one second (FEV_1) peak to be a short term effect, and advised that a bronchodilator response was not unexpected given that trial patients had been taking concomitant long-acting β adrenoceptor agonists (LABA), and that a longer period of follow-up may be required to detect an effect on exacerbations. FEV_1 peak had not previously been accepted as a measure for asthma; however trough FEV_1 had been accepted in the consideration of tiotropium in adults. Results of the secondary outcome of trough FEV_1 did not show any clinically significant value in either of the 6-11 or 12-17 year age group trials. The PBAC noted that a statistically significant reduction in the rate of symptomatic exacerbations (non-severe and severe) was only found in the trial for patients aged 6 to 11 years, which was due only to the reduction in non-severe symptomatic exacerbations. The PBAC noted that symptomatic exacerbations was not the usual trial measure for a study of long term treatment for asthma, and that severe exacerbations was used in the consideration of tiotropium in the adult population. The PBAC noted that the rate of severe exacerbations was marginally higher, but not statistically significant, in the tiotropium arms compared to the placebo arms in both trials. The PBAC noted that the strong placebo responses suggested that adherence to maximal optimal asthma therapy was poor prior to the trials, especially in the 12-17 year age group, concluding that the addition of tiotropium to the dosing regimen was not likely be the most clinically appropriate approach.
		Sponsor Comment:	The sponsor had no comment.

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TRAMADOL HYDROCHLORIDE WITH PARACETAMOL Tablet containing tramadol hydrochloride 37.5 mg with paracetamol 325 mg Zaldiar® Aspen Pharmacare Australia Pty Ltd New listing (Major Submission)	Acute and chronic pain	To request a Restricted Benefit listing for the treatment of acute and chronic pain where aspirin and/or paracetamol alone are inappropriate or have failed.	The PBAC did not recommend the fixed dose combination (FDC) of tramadol hydrochloride 37.5 mg with paracetamol 325 mg for patients with acute pain on the basis of extensive quality use of medicines problems, questionable clinical place for the FDC, an inappropriate comparator, and inadequately supported efficacy and safety compared with the relevant comparator. The PBAC considered there were significant quality use of medicines issues associated with dosing with the FDC and the potential for abuse. The PBAC considered that the nominated comparator (treatment likely to be replaced in practice) was not appropriate, and that comparative efficacy and safety against the appropriate comparator had therefore not been established. The PBAC considered that the savings claimed due to reduced adverse effects and GP visits were not well supported and are unlikely to be realised in practice.
		Sponsor Comment:	Aspen disagrees with the views expressed by the PBAC. Aspen continues to believe there is a clinical place for FDC's in acute pain management, in particular Zaldiar given its proven efficacy and superior ADRs/AEs profile compared to tramadol 50 mg IR capsules.