JULY 2018 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
BEZLOTOXUMAB Solution concentrate for I.V. infusion 1000 mg in 40 mL Zinplava® Merck Sharp & Dohme (Australia) Pty Ltd New listing (Major Submission)	Indicated for the prevention of recurrence of Clostridium difficile infection (CDI) in adult patients 18 years or older at high risk of recurrence of CDI who are receiving antibiotic therapy for CDI. ZINPLAVA is not indicated for the treatment of CDI. ZINPLAVA is not an antibacterial drug. ZINPLAVA should only be used in conjunction with antibacterial drug treatment of CDI.	BEZLOTOXUMAB is not currently PBS listed.	Resubmission to request a Section 100 Authority required listing for the treatment of patients at high risk of *Clostridium difficile* infection	The PBAC did not recommend the listing of bezlotoxumab on the PBS for the prevention of *Clostridium difficile* infection (CDI) on the basis of modest clinical benefit, uncertain and unfavourable cost-effectiveness, and considerable opportunity cost.
			Comparator: Placebo	The PBAC previously accepted that the comparator was placebo.
			Clinical claim: Superior comparative effectiveness and non-inferior comparative safety compared to placebo.	The PBAC accepted the claim of superior comparative efficacy of bezlotoxumab compared to placebo, although the PBAC considered that the magnitude of benefit was modest. The PBAC did not accept the claim of non-inferior comparative safety. The PBAC considered that a claim of inferior comparative safety would be more reasonable.
			Economic claim: Cost-effectiveness basis compared to standard of care (oral antibiotics)	The PBAC considered that the incremental cost effectiveness ratio (ICER) per quality adjusted life-year (QALY) presented in the submission was uncertain and likely an underestimate. The PBAC noted that the economic model was highly sensitive to the mortality and CDI recurrence rates, for which the available data was uncertain and variable. The PBAC also noted that the clinical trial data presented in the resubmission did not demonstrate a difference in mortality rates. The PBAC therefore considered that it would be appropriate to take a more conservative approach to the estimates of both baseline CDI recurrence and mortality, and the difference between placebo and bezlotoxumab with regard to these parameters. The PBAC defined a multivariate analysis that it considered to be more informative, and noted that the resulting ICER per QALY was >$200,000.
			Sponsor's comments:	The sponsor is disappointed in the PBAC outcomes for bezlotoxumab and is working with government towards making this treatment option available for patients with *Clostridium difficile* infection in Australia.

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EVOLOCUMAB Injection 140 mg in 1 mL single use pre-filled pen Injection 420 mg in 3.5 mL single use pre-filled cartridge Repatha® Amgen Australia Pty Ltd Change to listing (Major Submission)	Adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease (ASCVD) in combination with a statin or statin with other lipid lowering therapies, or in combination with other lipid-lowering therapies in patients who are statin-intolerant. Adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.	Familial homozygous hypercholesterolaemia	Resubmission to request an Authority Required listing to include the treatment of non-familial hypercholesterolaemia with atherosclerotic disease.	The PBAC did not recommend the listing of evolocumab for patients with non-familial hypercholesterolaemia with atherosclerotic disease on the basis of an inadequately defined patient population, an uncertain incremental cost-effectiveness ratio (ICER) and high and uncertain patient population numbers. The PBAC considered that this population required more refined eligibility criteria in the proposed PBS listing given the very high financial estimates. Following the publication of preliminary alirocumab data (from the ODYSSEY OUTCOMES trial) and the failure of the sponsor of evolocumab to provide an adequately defined population, the PBAC considered that a stakeholder meeting was required to establish a way forward for cost-effective use of drugs such as evolocumab (PCSK9 inhibitors) in the non-familial hypercholesterolaemia population.
			Comparator: Placebo and ezetimibe	The resubmission nominated both ezetimibe and placebo as the main comparators. The PBAC considered that these comparators were appropriate for the combined familial and non-familial hypercholesterolaemia submission in November 2017. However, for non- familial hypercholesterolaemia alone the PBAC were concerned that by nominating ezetimibe as a comparator, it would be replaced in the treatment algorithm by evolocumab.
			Clinical claim: Evolocumab was superior in terms of efficacy and similar in terms of safety compared to placebo and ezetimibe.	The PBAC reiterated that whilst the clinical claims were reasonable for low-density lipoprotein (LDL) reduction and time to first myocardial infarction, ischemic stroke or cardiac revascularisation based on the FOURIER trial, the patient populations that could benefit most from treatment were not identified by the sponsor.

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			Economic claim: Cost-utility analyses compared to ezetimibe and placebo.	The PBAC considered that the ICERs per quality adjusted life-year (QALY) presented in the submission for the comparisons with ezetimibe and placebo were uncertain. The PBAC noted the inclusion of a time lag between LDL reduction and impact on cardiovascular death, but were concerned about the magnitude of the reduction in cardiovascular mortality as this was a key driver of the economic model. The PBAC also reiterated that use of the cardiovascular outcomes data from the FOURIER trial would better inform the economic model.
			Sponsor's comments:	The sponsor has no comment
TEDUGLUTIDE Powder for injection 5 mg with diluent Revestive® Shire Australia Pty Limited New listing (Major Submission)	The treatment of adult patients with short bowel syndrome who are dependent on parenteral support. Patients should be stable on their parenteral support regimen for at least 4 weeks prior to initiating teduglutide.	Teduglutide is not currently PBS listed.	Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of short bowel syndrome (SBS) in patients who are dependent on parenteral nutrition for survival.	The PBAC did not recommend the listing of teduglutide for the treatment of patients with Type III (chronic) intestinal failure associated with short bowel syndrome on the basis that the patient group most likely to achieve a clinically meaningful benefit was unclear, the treatment duration required to achieve these benefits was unclear, and the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The PBAC recommended stakeholder consultation regarding the patient group most likely to benefit, criteria for stopping and continuing teduglutide and clarification of economic model parameters. The PBAC accepted the high clinical need and limited treatment options available for people with this condition.
			Comparator: Standard care	Accepted

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			Clinical claim: teduglutide plus standard care as superior in terms of effectiveness, and at least non-inferior in terms of safety compared to standard of care alone.	The PBAC re-iterated its previous advice that the claim of superior comparative effectiveness of teduglutide over standard care was reasonable, but considered there was a lack of long-term comparative clinical evidence to define the magnitude of the treatment effect associated with teduglutide. The PBAC re-iterated its previous advice that the claim of non-inferior safety of teduglutide over standard care was not adequately justified, particularly given the lack of comparative clinical data to support the claim of reduced parenteral support complications.
			Economic claim: cost utility analysis of teduglutide plus standard care compared to standard care alone	The PBAC considered that the incremental cost-effectiveness ratio (ICER) presented in the resubmission was uncertain because the economic model: did not allow a placebo response; included distant and uncertain price reductions in the base case; and included carer disutilities in the base case rather than a supplementary analysis. The PBAC considered that the economic model should also be updated to incorporate the impact of the stopping rule and continuation criteria (when finalised). The PBAC also considered that the ICER was unacceptably high (>$200,000/QALY in the resubmission base case).
			Sponsor's comments:	Shire will work with the Department of Health and the PBAC so that patients with this rare disease are able to access teduglutide treatment in Australia.