JULY 2011 PBAC MEETING OUTCOMES - "Subsequent" decisions not to recommend

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
AGOMELATINE, tablet, 25mg, Valdoxan® Servier Laboratories (Australia) Pty Ltd Major submission	Treatment of major depression in adults including prevention of relapse.	Not currently PBS listed		The PBAC rejected the submission on the basis that superior clinical effectiveness and safety over selective serotonin reuptake inhibitors (SSRIs) had not been demonstrated.
			Listing requested: Restricted Benefit listing for major depressive disorders.	The PBAC considered the listing requested was appropriate.
			Comparator: Venlafaxine was the primary comparator. A comparison of agomelatine with SSRIs, fluoxetine, sertraline and escitalopram was also presented.	The PBAC considered that the SSRIs were the more appropriate main comparator for agomelatine as agomelatine will be used in the first line treatment of depression and is more likely to substitute for SSRIs than the more expensive SNRIs in clinical practice.
			Clinical claim: Agomelatine is non-inferior in terms of efficacy and superior in terms of discontinuation from treatment to the primary comparator venlafaxine.	The PBAC considered that substantiation of a claim of non-inferiority to venlafaxine firstly requires demonstration of superiority over the SSRIs. The PBAC further considered that the evidence provided in the submission was not sufficient to support the claim that agomelatine was superior in terms of comparative efficacy and safety to the SSRIs.
			Economic claim: The submission presented a cost	The PBAC noted uncertainties regarding both the equi-effective

			minimisation analysis versus venlafaxine.	doses of agomelatine and venlafaxine and the updated model which was still based on the clinical claim that fewer discontinuations would occur with agomelatine compared to venlafaxine. These fewer discontinuations were assumed to translate to better adherence, a claim that has not previously been accepted by PBAC.
			Sponsor's comments:	Servier have met with the PBAC Chairman and are working towards ensuring Australians have equitable access to agomelatine in a timely manner.

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COLISTIMETHATE SODIUM, powder for nebuliser solution, 1 million IU (equivalent to 80 mg colistimethate sodium), Tadim® Phebra Pty Ltd Minor submission	For the treatment of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Not currently PBS listed		The PBAC rejected the submission on the basis of uncertain clinical benefit and inadequate evidence of cost effectiveness.
			Listing requested: Authority required listing for treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis.	The PBAC considered the listing requested was appropriate.
			Comparator: Nebulised tobramycin.	The PBAC noted that the algorithm of choice for management of chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis was one of nebulised tobramycin alternating monthly with nebulised colistimethate.
			Clinical claim: Colistimethate sodium is no worse than tobramycin by nebulisation when used for the treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis.	The PBAC noted that tobramycin solution for inhalation, single dose units, 300 mg in 5 mL (Tobi®) was recommended on a month on/month off basis. The submission stated that, to the knowledge of the sponsor, there was no published clinical trial completed or underway assessing the efficacy of this alternating regimen nor was one likely to be completed with sufficient power to inform this decision. The PBAC considered the clinical

				benefit of colistimethate uncertain.
			Economic claim: A cost minimisation analysis against tobramycin solution for inhalation, single dose units, 300 mg in 5 mL (Tobi®) was presented.	Although presented as a cost minimisation analysis against nebulised tobramycin, an alternating regimen using the two nebulised antibiotics would markedly increase costs for unknown extra benefit over the month on month off tobramycin recommendation. The PBAC considered that there was no clinical evidence to assess cost-effectiveness within the clinical paradigm in which this drug will be used i.e. month on month off alternating with tobramycin.
			Sponsor's comments:	The sponsor has no comment.

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ICATIBANT, injection, 30 mg in 3 mL (as acetate), single use pre-filled syringe, Firazyr® Shire Australia Pty Ltd Major submission	For symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).	Not currently PBS listed		The PBAC rejected the submission on the basis that uncertainty remained over the extent of clinical benefit in the self-administration setting and on the basis of the resultant uncertain, as well as unacceptably high, cost effectiveness ratio.
			Listing requested: Authority Required listing for anticipated emergency treatment of an acute attack hereditary angioedema in a patient with confirmed diagnosis of C1-esterase inhibitor deficiency.	The PBAC noted that the revised requested PBS restriction no longer specified either the site (i.e. cutaneous, abdominal or laryngeal) or the severity of an attack to be treated with icatibant. Patients who self-administer icatibant are provided with a treatment action plan to ensure appropriate use. Despite acknowledging the good intent of the proposed emergency action plan, the PBAC considered that there would be a high risk that patients would use icatibant where symptoms are milder than in the intended population. The PBAC also noted, as with the previous submission, that the proposed clinical management algorithm with icatibant is more restrictive than that published in the Australian Society of Clinical Immunology and Allergy (ASCIA) position paper on hereditary angioedema (Katelaris 2010). Thus,

				there was considerable doubt whether icatibant would be used in practice according to the requested restriction and the proposed clinical management algorithm.
			Comparator: Placebo as proxy for “best supportive care, with delayed use of C1 esterase inhibitor (C1-INH) concentrate if required”.	The PBAC accepted the proposed comparator of best supportive care and C1-INH concentrate if required. It was noted however, that the trials were placebo controlled and thus placebo was nominated as a proxy for best supportive care (BSC). BSC differs depending on the nature of the HAE attack: • For laryngeal - BSC includes admission and C1-INH as soon as possible • For severe or progressive (abdominal) - admission and C1-INH • For other attacks, including abdominal - analgesia, rest and observation. The PBAC noted that use of pain medication in the trials was restricted for 8-9 hours which is not reflective of Australian clinical practice. Thus, the use of placebo as a proxy for best supportive care was considered uncertain and would likely overestimate the benefit of icatibant.
			Clinical claim: Icatibant is superior in terms of efficacy over placebo and inferior in terms of	The PBAC accepted, on the basis of the clinical trials presented in the submission, that icatibant is superior

			safety.	in terms of efficacy over placebo. However, the applicability of these results to the requested PBS population remained uncertain. The PBAC accepted the claim that icatibant is inferior in terms of comparative safety over placebo.
			Economic claim: The re-submission presented a modelled cost-effectiveness analysis of self-administered icatibant versus best supportive with delayed use of C1-INH concentrate if required.	The PBAC noted that the outcome of the economic evaluation was largely dependent on the difference in the utility weight for the attack-free health state between the two treatment arms, as elicited in the scenario-based utility valuation study presented in the submission. The PBAC considered that there were a number of uncertainties about the results of this study and overall, the PBAC was of the view that the scenarios used in the utility study were not adequately supported. Further uncertainty arose because attack treatment algorithm variables used in the model were based on the outcomes of trials performed in the hospital setting, the applicability of which to the self-administration setting remained uncertain.
			Sponsor's comments:	Shire appreciates that the PBAC recognises the there is a high unmet clinical need on the PBS for an effective treatment in this patient population and Shire welcomes the

				opportunity to work constructively with the PBAC towards a quick resolution to make this product available. Shire thanks the PBAC for their open and ongoing dialogue.

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LENALIDOMIDE, capsule, 5 mg and 10 mg,Revlimid® Celgene Pty Ltd Minor submission	For use in combination with dexamethasone in patients with multiple myeloma whose disease has progressed after one therapy. For treatment of patients with transfusion-dependent anaemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.	Monotherapy or in combination with dexamethasone, of patients with a histological diagnosis of multiple myeloma who have progressive disease after at least 1 prior therapy and who have undergone or are ineligible for a primary stem cell transplant.		The PBAC rejected the submission on the basis of a high and uncertain cost-effectiveness ratio.
			Listing requested: Extend the current Section 100 (Highly Specialised Drugs Program) Authority required listing to include use in the treatment of patients with transfusion dependent low risk/INT-1-5q myelodysplastic syndrome.	The PBAC agreed with the definition of transfusion dependence which requires patients to have received at least 8 units of red cells over the most recent 6 months prior to requesting access to lenalidomide on the PBS, but considered that the following wording should be added “and would be expected to continue this requirement without lenalidomide treatment.” The PBAC further considered that inclusion of continuing treatment criteria would be necessary.
			Comparator: The submission nominated placebo (best supportive care) as the main comparator.	The PBAC considered this appropriate.
			Clinical claim: Lenalidomide is superior in terms of comparative effectiveness and associated with more toxicity over best supported care.	The PBAC considered this reasonable (no new data were presented in the re-submission).

			Economic claim: Cost effectiveness. The basis and structure of the economic model for lenalidomide were unchanged from those considered by the PBAC at the March 2011 meeting.	The PBAC noted that the re-submission recalculated the ICER using the Szende utilities at the lower price proposed. The PBAC considered that by using the same utilities to recalculate the ICER but at the reduced price, the estimated ICER was still high and uncertain. The PBAC further noted that there was no modelling of a continuation rule in the economic model, in which there is a 50 % reduction in transfusions, and therefore the risk of non cost-effective continuation of lenalidomide long term had not been dealt with in economic model. A continuation rule would be necessary to deal with this uncertainty and treatment beyond one year would require complete or near transfusion independence. The PBAC considered that prescribers would need to affirm that transfusion requirements have reduced by 50 % at least after 4 and 8 months.
			Sponsor's comments:	Celgene disagrees with the decision and sympathises with patients that will not be able to access Revlimid for MDS.

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LIRAGLUTIDE (rys), solution for injection, 3 mL pre-filled injection pen, 6 mg per mL, Victoza® Novo Nordisk Pharmaceuticals Pty Ltd Minor submission	Liraglutide is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control: • in dual combination, added to metformin or a sulphonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulphonylurea monotherapy. • in triple combination, added to metformin and a sulphonlyurea in patients with insufficient glycaemic control despite dual therapy.	Not currently PBS listed.		The PBAC rejected the submission on the basis of uncertain cost effectiveness.
			Listing requested: Re-submission for an Authority required listing for treatment of type 2 diabetes: 1) as triple combination therapy with metformin and a sulphonylurea; 2) as dual combination therapy with metformin or a sulphonylurea in patients for whom a combination of metformin and a sulphonylurea is contraindicated or not tolerated.	The PBAC considered the listing requested was appropriate.
			Comparator: Exenatide	The PBAC considered exenatide to be the appropriate comparator.
			Clinical claim: Liraglutide is superior in terms of comparative effectiveness and equivalent in terms of comparative safety to exenatide.	The PBAC accepted that the difference between the two arms of the pivotal trial of 0.33 % change in HbA1c, favouring liraglutide compared to exenatide, to be marginally clinically meaningful. The PBAC however noted that the mean difference could be as low as -0.18%, based on the upper limit of the 95 % confidence interval.
			Economic claim: Cost effectiveness. The submission	The PBAC considered the cost effectiveness uncertain. One area of

			presented the same modelled economic evaluation as previously, with some variables changed, using the CORE Diabetes Model to project the long-term outcomes of treatment. The type of economic evaluation presented was a cost-utility analysis.	uncertainty not addressed was that, as previously, the model was based on a difference between the two arms of the pivotal trial of -0.33% in HbA1c, favouring liraglutide. Acceptance of the resubmission's economic analysis also relied on the validity of the treatment duration in the model.
			Sponsor's comments:	Novo Nordisk is disappointed with the PBAC's recommendation but will continue to work constructively with the PBAC to ensure that liraglutide is made available for patients and physicians dealing with the burden of type 2 diabetes as soon as possible.