JULY 2012 PBAC MEETING OUTCOMES - "Subsequent" decisions not to recommend

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, lyophilised powder for injection, 100 units, Botox® Allergan Pty Ltd Major submission	Prophylaxis of headaches in adults with chronic migraine (headache on at least 15 days per month of which at least 8 days are with migraine). Botulinum toxin type A purified neurotoxin complex is also TGA registered for the following indications: • Blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and over; • Cervical dystonia (spasmodic torticollis); • Dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two	Section 100 Botulinum Toxin Program Criteria for availability: Treatment of blepharospasm associated with dystonia; Treatment of dynamic equinus foot deformity; Treatment of spasmodic torticollis; Treatment of moderate to severe spasticity of the upper limb; Treatment of moderate to severe spasticity of the upper limb in adults following a stroke; Treatment of severe primary axillary hyperhidrosis.		The PBAC rejected the re-submission on the basis of uncertain cost-effectiveness, due to uncertainty in the economic analysis associated with the fee to administer botulinum toxin, the assumption that all patients experiencing less than a 50% reduction in headache days would discontinue treatment, and the extrapolation of the trial data to a 5-year time horizon with a sustained treatment effect for responders.
			Listing Requested: Section 100 Botulinum Toxin Program Authority Required Prophylaxis of headaches in an adult patient with chronic migraine who fulfil the following criteria: 1. Patient has experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months 2. Inadequate response, intolerance or contraindication to at least three migraine prophylactic medications. Treatment should be discontinued if the patient does not respond after two treatments.	The PBAC noted the requested restriction was more restrictive than the previous submission. However, the PBAC considered the criteria used for assessment of response are highly subjective and there would be considerable risk of use outside the requested restriction in 'partial responders'. The PBAC also considered there was risk of usage beyond the subjective initiation rules relating to type of headache, number of headache days and number of previous prophylactic medicines.

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	years of age or older; • Focal spasticity in adults; • Strabismus in children and adults; and • Focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years of age and older. • severe primary hyperhidrosis of the axillae • Spasmodic dysphonia Botulinum toxin type A purified neurotoxin complex is indicated for the following cosmetic indications: Temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults		Comparator: Best Supportive Care (BSC), consisting of no further prophylaxis but with continuation of acute headache pain medications as required.	The PBAC agreed that the nominated comparator was appropriate for the population meeting the requested restriction.
			Clinical claim: The re-submission, consistent with the previous submission, claimed that Botox is superior to BSC in terms of efficacy, and inferior in terms of safety.	The PBAC accepted that a reduction of 2-3 headache days per month could be considered a clinically important benefit. The PBAC previously found the claim of inferiority for comparative safety to be reasonable.
			Economic claim: Updated modelled economic evaluation (Cost Utilisation Analysis) based on the claim of superior efficacy	The PBAC noted the model had been updated to reflect changed continuation criteria and reduced cost of treatment. However, the model did not include changes to other parameters previously identified by PBAC as being of concern. These were addressed in sensitivity analyses.
			Sponsor's comments:	Allergan is disappointed with the decision and will work with the PBAC to find ways to make Botox® available on the PBS to patients with chronic migraine.

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PLERIXAFOR, solution for injection, 20 mg in 1 mL, 1.2 mL, Mozobil® Sanofi Aventis Australia Pty Ltd Major submission	Use in combination with granulocyte-colony stimulating factor (GCSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.	Not currently PBS listed		The PBAC rejected the submission on the basis of a high and uncertain cost-effectiveness ratio.
			Listing Requested: Section 100 (Highly Specialised Drugs Program) Private Hospital Authority Required and Public Hospital Authority Required (Streamlined) listing for: 1.Treatment, in combination with a granulocyte-colony stimulating factor (G-CSF), of lymphoma in patients who require autologous stem cell transplantation and who have failed previous stem cell collection or who are failing a current stem cell collection. 2.Treatment, in combination with a granulocyte-colony stimulating factor (G-CSF), of multiple myeloma in patients who require autologous stem cell transplantation and who have failed previous stem cell collection or who are failing a current stem cell collection.	The PBAC noted that the proposed restriction had been revised to specify the inclusion of patients who are failing a current stem cell collection (i.e. immediate rescue), as well as patients who have failed previous stem cell collection. The PBAC considered that it was important that the restriction include a definition of the patient groups, including CD34+ thresholds.

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			Comparator: G-CSF in combination with chemotherapy (ifosfamide + carboplatin + etoposide for lymphoma; and cyclophosphamide for multiple myeloma) in treating patients with lymphoma and multiple myeloma who have failed previous stem cell collection attempts.	Accepted previously by the PBAC.
			Clinical claim: Plerixafor administered in conjunction with G-CSF can be an effective means to salvage patients who had previously failed standard mobilisation attempts, or are in the process of failing a current attempt.	The PBAC considered the claim of efficacy over the comparator was reasonable, but the magnitude of the benefit remained uncertain.
			Economic claim: Modelled cost-effectiveness analysis	The PBAC considered the cost-effectiveness of plerixafor is dependent on being able to target treatment to the most appropriate patients.
			Sponsor's comments:	Sanofi is disappointed the PBAC has not recommended Mozobil for listing on the PBS. Sanofi remains committed to working with the PBAC to ensure that Mozobil is made available on the PBS for the patients with multiple myeloma or lymphoma undergoing stem cell mobilization.

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PRUCALOPRIDE, tablet, 1 mg and 2 mg (as succinate), Resotrans® Janssen-Cilag Pty Ltd Major submission	Treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief. Before prucalopride is considered patients must have tried at least two different types of laxatives from different classes (at the highest tolerated recommended doses) for at least 6 months, but have not had adequate relief from constipation. If treatment with prucalopride is not effective within 4 weeks, the benefit of continuing treatment should be reconsidered.	Not currently PBS listed		The PBAC rejected the re-submission on the basis of uncertain magnitude of clinical benefit and uncertain cost-effectiveness.
			Listing Requested: Restricted benefit listing for the treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief. Before prucalopride is considered patients must have tried at least three different types of laxatives from different classes (such as bulk forming agents, osmotic laxatives, stimulant laxatives) for at least six months but have not had adequate relief from constipation.	The PBAC considered there was considerable potential for use beyond the intended population as no definition of 'adequate response' was included in the restriction and it was likely that patients who experience a partial benefit will continue therapy. The PBAC noted that the sponsor's pre-PBAC response proposed an Authority Required restriction where diagnosis, initiation and initial assessment for continuing treatment be made by, or in consultation with a gastroenterologist.
			Comparator: Best supportive care (BSC) re-defined as stimulant laxatives in patients who have failed to achieve adequate relief with bulk forming agents, osmotic laxatives and stimulant laxatives.	The PBAC considered the revised definition of BSC was a reasonable comparator for the proposed PBS population, noting that this definition of BSC only accounts for oral treatments and excludes enemas.

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			Clinical claim: Prucalopride + best supportive care is superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo + best supportive care.	The PBAC considered that the inclusion of a new trial in a meta-analysis did not substantially change the basis for the PBAC's conclusion from the November 2011 submission of uncertain clinical effectiveness in the requested PBS population. The PBAC had previously accepted that prucalopride plus BSC was inferior in terms of comparative safety over placebo plus BSC.
			Economic claim: Revised modelled evaluation.	The PBAC considered there were a number of issues with the economic model which contributed to uncertainty in the ICER.
			Sponsor's comments:	Janssen acknowledges the concerns of the PBAC and will continue to work with the PBAC towards achieving a positive recommendation for prucalopride.

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RIFAXIMIN, tablet, 550 mg, Xifaxan® Norgine Pty Ltd Major submission	Prevention of the recurrence of hepatic encephalopathy (HE) where other treatments have failed or are contraindicated.	Not currently PBS listed		The PBAC rejected the submission on the basis of high, uncertain, and unacceptable cost effectiveness.
			Listing Requested: Restricted benefit listing for the prevention of hepatic encephalopathy in adult patients who have had prior episodes of hepatic encephalopathy. Treatment is to be in combination with lactulose where lactulose therapy can be tolerated.	As previously, the PBAC noted that the patient population in the pivotal trial is narrower than the requested PBS population as it precludes patients who will be eligible for treatment with rifaximin under the proposed PBS restriction.
			Comparator: Lactulose alone (or placebo).	Accepted (as previously).
			Clinical claim: Rifaximin is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.	The PBAC reiterated that the magnitude of the treatment effect was uncertain and further considered that it may be an overestimate of the effect of rifaximin in clinical practice. The PBAC remained concerned that there is potential for development of antibiotic resistance with use of rifaximin.
			Economic claim: Updated modelled cost-utility analysis based on superiority claims over placebo.	The PBAC considered that the economic claim was not supported by the data presented.
			Sponsor's comments:	The sponsor has no comments.

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SAPROPTERIN, soluble tablet, 100 mg (as dihydrochloride), Kuvan® Merck Serono Australia Pty Ltd Major submission	Treatment of hyperphenylalaninaemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency.	Not currently PBS listed		The PBAC rejected the submission for listing on the PBS as it would not be considered cost-effective. The PBAC was satisfied that the submission appropriately addresses and fulfills the LSDP criteria. The PBAC deferred the submission so that further discussion could take place with the sponsor.
			Listing Requested: Section 100 (Highly Specialised Drugs Program) Authority Required Treatment of hyperphenylalaninaemia (HPA) in a patient demonstrated to have tetrahydrobiopterin (BH4) deficiency If rejected, Life Saving Drugs Program (LSDP) listing for BH4 deficiency is requested.	
			Comparator: No treatment with sapropterin in the treatment of HPA in patients demonstrated to have BH4 deficiency and prior treatment with other synthetic BH4 for patients with BH4 deficiency.	The PBAC previously agreed that the appropriate comparator for patients with BH4 deficiency is prior treatment with sapropterin.

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			Clinical claim: Sapropterin as more effective than placebo and at least as effective as other synthetic BH4 formulations in the long term treatment of BH4 deficiency	The PBAC concluded that appropriate treatment with sapropterin, perhaps in combination with neurotransmitter precursors (L-DOPA or 5-HT) may lead to normal physical, intellectual and psychomotor development and life extension beyond infancy in paediatric patients with BH4 deficiency. Due to limited data available in adult patients the benefit of treatment with sapropterin for adult and elderly patients is uncertain.
			Economic claim: Indicative evaluation of the cost per life year gained. The submission claimed that sapropterin is not cost effective.	The PBAC considered that due to the high cost of sapropterin it would not be considered cost effective for listing on the PBS. The PBAC considered the inclusion of sapropterin on the LSDP.
			Sponsor's comments:	Merck Serono is pleased to continue working with the PBAC and the Department to ensure timely access to Kuvan, through the LSDP, for patients with this rare and serious condition.

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SUNITINIB, capsule, 12.5 mg, 25 mg, 50 mg (as malate), Sutent® Pfizer Australia Pty Ltd Minor submission	Treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET). Sunitinib is also registered for the treatment of advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance.	Authority required Initial treatment and continuing treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients meeting certain criteria. Authority required Initial and continuing treatment of metastatic or unresectable malignant gastrointestinal stromal tumour in patients meeting certain criteria.		The PBAC rejected the submission on the basis of an unacceptably high and uncertain ICER compared to best supportive care (placebo).
			Listing Requested: Extend the current Authority Required listing to include initial and continuing treatment of metastatic, unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (or carcinoma) (pancreatic NET) in patients who are symptomatic (despite somatostatin analogues) or who have documented disease progression.	
			Comparator: Best Supportive Care (placebo)	Accepted (as previously)
			Clinical claim: Nil	The PBAC previously accepted that sunitinib is likely to have some survival benefit, but the size of the effect is unknown.
			Economic claim: Updated trial-based and modelled economic evaluations.	The PBAC considered that even when taking into account the revised price the ICER remained unacceptably high.
			Sponsor's comments:	Pfizer is disappointed by the decision, but will continue to work with the PBAC to make sunitinib available for this patient population

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TAPENTADOL, tablet, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg (as hydrochloride) (sustained release), Palexia SR® CSL Biotherapies (CSL Limited) Minor submission	The management of moderate to severe chronic pain un-responsive to non-narcotic analgesia. There is currently no clinical data available regarding the safety and efficacy of tapentadol SR in patients with pain due to malignancy.	Not currently PBS listed		The PBAC rejected the submission because of uncertain clinical need, high cost and therefore uncertain cost-effectiveness.
			Listing Requested: Restricted benefit Chronic severe disabling pain not responding to non-narcotic analgesics.	The PBAC noted that there are many products for management of severe pain already listed on the PBS, and therefore it is difficult to determine whether there is a significant clinical need for tapentadol.
			Comparator: Oxycodone CR as the main comparator and tramadol SR as a secondary comparator.	Accepted (as previously).
			Clinical claim: Tapentadol SR is equivalent to oxycodone CR in terms of analgesic efficacy and superior to oxycodone CR in terms of adverse event rates related to constipation and nausea/vomiting. Tapentadol SR is at least non-inferior to tramadol SR in terms of analgesic efficacy and non-inferior to tramadol SR in terms of safety.	The PBAC accepted previously the clinical claim of comparative effectiveness compared with oxycodone CR but not the claim of superior safety. The PBAC remained uncertain of how to value any difference in the rate of adverse effects. The PBAC accepted previously the claim of non-inferiority in terms of comparative effectiveness and safety compared with tramadol SR was accepted.

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			Economic claim: Updated cost utility analysis versus oxycodone CR Updated cost-minimisation analysis versus tramadol SR	The PBAC considered that the ICERs in the cost utility analysis remained difficult to interpret and the estimation of the equi-effective dose remained uncertain in the cost-minimisation analysis.
			Sponsor's comments:	CSL disagrees with the PBAC's decision, but is committed to working with the PBAC to ensure tapentadol SR is available for patients with chronic severe disabling pain not responding to non-narcotic analgesics.