NOVEMBER 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
ALGLUCOSIDASE alfa-rch, powder for I.V infusion, 50 mg, Myozyme® Genzyme (Sanofi-Aventis Australia Pty Ltd) Major submission	Long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).	Not currently PBS listed. Alglucosidase is funded under the Life Saving Drugs Program (LSDP) for the treatment of infantile onset Pompe disease.		The PBAC rejected the submission on the basis of uncertainty about whether the lifespan of a patient with late onset Pompe disease would be substantially extended as a direct consequence of using alglucosidase alfa.
			Listing Requested: The submission sought a recommendation from PBAC that alglucosidase should be included in the LSDP for the treatment of late onset Pompe disease. The sponsor did not propose wording for a PBS listing.	
			Comparator: Standard (palliative) therapy including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services.	Accepted as previously.
			Clinical claim: Alglucosidase alfa significantly increases survival in patients with late-onset Pompe disease.	Not accepted.
			Economic claim: The submission did not present an economic evaluation.	The PBAC has previously accepted that alglucosidase alfa is not cost effective for PBS

				listing.
			Sponsor's comments:	Genzyme is disappointed with the PBAC recommendation but is committed to working with the PBAC and the LSDP to ensure access for patients.
BUDESONIDE with EFORMOTEROL FUMARATE DIHYDRATE, oral pressurised inhalation, 50 mcg – 3 mcg per dose, 100 mcg– 3 mcg per dose, 200 mcg – 6 mcg per dose, Symbicort Rapihaler® AstraZeneca Pty Ltd Minor submission	Asthma: treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta 2-agonist) is appropriate in adults and adolescents. This includes patients who are symptomatic on inhaled corticosteroid therapy; patients who are established on regular long acting beta 2-agonist and inhaled corticosteroid therapy. There are two alternative treatment regimens: Symbicort maintenance and reliever therapy (SMART); and Symbicort maintenance therapy. The 200-6 strength should not be used for the SMART regimen.	Not currently listed. Symbicort Turbuhaler's PBS listing can be viewed at the following website: www.pbs.gov.au		The PBAC rejected the submission on the basis that no data were presented to determine the efficacy or safety of the 50-3 mcg and 100-3 mcg Rapihaler presentations in the indications requested for PBS listing or the 200-6 mcg Rapihaler in the asthma indication, that the cost effectiveness of Symbicort Rapihalers over Seretide® metered dose inhalers in the requested indications had not been demonstrated and on the basis of uncertain utilisation and costs to the PBS.
			Listing requested: The submission sought the same asthma and COPD PBS indications as Symbicort Turbuhaler®.	
			Comparator: Symbicort Turbuhaler products and fluticasone with salmeterol (Seretide®) pressurised metered dose inhaler products.	Accepted.

	Chronic Obstructive Pulmonary Disease (COPD): Symbicort 200/6 is indicated for the symptomatic treatment of moderate to severe COPD (Forced Expiratory Volume in 1 second (FEV1) less than or equal to 50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbation. Symbicort is not indicated for the initiation of bronchodilator therapy in COPD.		Clinical claim: A clinical need exists for a pressurised metered dose inhaler presentation of the current dry powder breath actuated device.	No clinical data were presented in the current submission for the asthma indication.
			Economic claim: The submission did not provide an economic evaluation. The requested prices for the Rapihaler products were equivalent to the Turbuhaler products.	The PBAC considered that any future submission should take the form of a major submission. The PBAC considered that the submission provided insufficient evidence to justify the proposed substitution patterns and the price advantage that would exist for Symbicort Rapihaler products compared to the lowest and highest strengths of Seretide products.
			Sponsor's comments:	AstraZeneca will continue to work towards PBS listing for Symbicort Rapihaler.
EZETIMIBE and ATORVASTATIN, pack containing 30 tablets ezetimibe 10 mg, and 30 tablets atorvastatin 10 mg (as calcium), atorvastatin 20 mg (as calcium), atorvastatin 40 mg (as calcium) or atorvastatin 80 mg (as calcium), Atozet Composite Pack®	At the time of PBAC consideration, Atozet Composite Pack's TGA registration was yet to be finalised.	Not currently listed. See www.pbs.gov.au for ezetimibe's and atorvastatin's PBS listings.		The PBAC rejected the submission on the basis that the co-pack provided no demonstrated clinical or convenience advantage to consumers, the potential increase in cost to Government and the lack of evidence that the composite combination pack would be used appropriately. The PBAC considered that the issues outstanding would be most

Merck Sharp & Dohme (Australia) Pty Ltd Minor submission				appropriately addressed in a major submission.
			Listing requested: Authority Required (Streamlined) listing for the treatment, in conjunction with dietary therapy and exercise, of a patient whose cholesterol levels are inadequately controlled with a statin and who meet certain criteria.	
			Comparator: The corresponding doses of ezetimibe and atorvastatin taken concomitantly was the main comparator. Ezetimibe with simvastatin was a secondary comparator.	Accepted.
			Clinical claim: The ezetimibe and atorvastatin composite packs will provide alternative therapy to patients already taking ezetimibe with simvastatin FDC products, ezetimibe and atorvastatin as individual products concomitantly and ezetimibe and rosuvastatin as individual products concomitantly.	The PBAC was not satisfied that the ezetimibe and atorvastatin composite pack meets the minimum requirements as set out in Part IV of the PBAC Guidelines for combination products.
			Economic claim: No economic analysis was presented.	
			Sponsor's comments:	The sponsor has no comment.

GEFITINIB, tablet, 250 mg, Iressa® AstraZeneca Pty Ltd Major submission	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), whose tumours express activating mutations of the EGFR TK (tyrosine kinase).	Authority Required Initial PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients where disease progression has occurred following treatment with at least 1 chemotherapy agent and who meet certain criteria. Authority Required Continuing PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients meeting certain criteria. See www.pbs.gov.au for full details.		The PBAC rejected the submission on the basis of unacceptably high and uncertain cost-effectiveness, and noting also the expected lack of any overall survival gain for patients resulting from the proposed extended listing and that there is currently insufficient confidence in the accuracy of EGFR test results.
			Listing requested: Extend the current Authority Required listing to include first line treatment of locally advanced or metastatic NSCLC in a patient who meets certain criteria and to increase in the current number of repeats from 3 to 5.	The PBAC formed the view that future applications for gefitinib should consider a restriction to EGFR mutation positive patients but without specifying line of therapy. The PBAC also considered alignment of gefitinib and erlotinib restrictions to be clinically appropriate, so that the existing second-line PBS listing of erlotinib would need to be reconsidered and adjusted to restrict its availability on the PBS to patients with an EGFR activating mutation.
			Comparator: Platinum-based doublet chemotherapy with carboplatin and paclitaxel.	Accepted as previously.
			Clinical claim: The resubmission described EGFR mutation testing and treatment of EGFR	The PBAC considered that the clinical benefit of listing gefitinib as first-line treatment in addition

			mutation positive patients with gefitinib as superior in terms of progression free survival and non-inferior in terms of overall survival compared to platinum-based doublet chemotherapy. The resubmission also described gefitinib as superior in terms of comparative safety over platinum-based doublet chemotherapy.	to second-line treatment is an improvement in quality of life, but not a prolongation of life.
			Economic claim: Modelled economic evaluation (cost-utility analysis) of the cost-effectiveness of the proposed scenario (both first-line EGFR testing and gefitinib are available) over the current scenario (neither first-line EGFR testing nor first-line gefitinib is available).	Not accepted. The PBAC had concerns with the validity of various assumptions and parameters used in the economic model.
			Sponsor's comments:	AstraZeneca acknowledges the complexity of this co-dependent submission and will continue to work with the PBAC and Medical Services Advisory Committee (MSAC).
IVABRADINE, tablet, 5 mg and 7.5 mg (as hydrochloride), Coralan® Servier Laboratories (Australia) Pty Ltd Minor submission	Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm, who are unable to tolerate or have a contraindication to the use of beta-blockers, OR in combination with atenolol 50 mg once daily when	Not currently listed.		The PBAC rejected the submission on the basis of uncertain clinical benefit in patients with symptomatic systolic heart failure and resulting uncertain cost-effectiveness.
			Listing requested: <u>Authority Required</u> Treatment of symptomatic systolic heart failure in patient in sinus rhythm, with	The PBAC considered the proposed listing would be difficult to implement in practice because although heart rate can be

	heart rate is at or above 60 beats per minute (bpm) and angina is inadequately controlled. Treatment of symptomatic chronic heart failure of New York Heart Association Classes II or III and with documented left ventricular ejection fraction less than or equal to 35% in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.		heart rate of at least 77 bpm, measured after 5 minutes rest, who is stabilised on optimal heart failure therapy, which must include an ACE inhibitor, or angiotensin II antagonist and a beta-blocker, if tolerated, or, in a patient who has a contraindication and/or intolerance to beta-blockers as described in the relevant TGA-approved Product Information.	accurately measured, the PBAC considered that heart rate can vary in individuals at any time and so it would be difficult to restrict use of ivabradine to patients with a heart rate greater than 77 bpm.
			Comparator: Placebo (standard medical management).	Accepted.
			Clinical claim: The submission described ivabradine as superior in terms of comparative benefit and equivalent in terms of comparative safety over placebo for patients with a baseline heart rate of ≥75 bpm.	The PBAC considered there to be uncertain clinical benefit. In July 2012 the PBAC had accepted that there may be evidence of a benefit associated with ivabradine treatment in a small sub-group of patients, but remained concerned that this effect is statistically significant in a subgroup only, and that it is driven by events related to hospitalisation.
			Economic claim: Cost-effectiveness compared to placebo.	Not accepted.
			Sponsor's comments:	Servier Australia will continue to work with the Pharmaceutical Evaluation Branch and the PBAC to make ivabradine available for Australian patients suffering from heart failure.

NAPROXEN with ESOMEPRAZOLE, tablet, 500 mg – 20 mg (as magnesium trihydrate), Vimovo® AstraZeneca Pty Ltd Minor submission	Patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component and in whom lower doses of naproxen or other NSAIDs have proven insufficient. If a total daily dose of 1 gram naproxen is not required, Vimovo should not be used.	Not currently PBS listed.		The PBAC rejected the submission on the basis that criteria for listing combination products are not all met.
			Listing requested: <u>Restricted Benefit</u> Symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires a non-steroidal anti-inflammatory (NSAID) and is at an increased risk of gastrointestinal ulceration in whom lower doses of naproxen or other NSAIDs are insufficient.	Criterion (b) in Part IV of the PBAC Guidelines requires that "the component products should preferably be on the PBS". The PBAC noted that although both components are PBS-listed, esomeprazole is not PBS-subsidised for prevention of gastrointestinal complications resulting from therapy with non-steroidal anti-inflammatory drugs (NSAIDs). It was also noted that criterion (c) also requires that "restrictions for the component products should be consistent with those proposed for the combination". The PBAC requested the Secretariat to provide an update of the current restrictions and utilisation for the entire class of drugs.
			Comparator: A mixed comparator of celecoxib and meloxicam.	The PBAC agreed that these were the appropriate comparators.
			Clinical claim: Naproxen/esomeprazole fixed dose combination (FDC) is non-inferior to the	The PBAC recalled its March 2012 advice, that overall, there was insufficient evidence to

			mixed comparator in terms of comparative effectiveness on all primary (pain and function) measures and non-inferior in a number of gastrointestinal safety and tolerability measures. Naproxen/esomeprazole FDC is superior to naproxen for the incidence of endoscopically detected ulcers.	establish that observed differences in the surrogate outcome, endoscopically-detected ulcers, accurately predicts the extent of differences in the risk of clinically relevant changes in symptomatic gastrointestinal events. The PBAC was unconvinced by the additional justification given in the re-submission for using endoscopically-detected ulcers as a surrogate outcome to establish non-inferiority.
			Economic claim: Cost-minimisation against a mixed comparator of meloxicam and celecoxib with a revised pricing proposal.	Not accepted. The PBAC considered there to be continuing uncertainty regarding the validity of the surrogate outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes, and the resultant impact on the cost-minimisation analysis. The PBAC considered that the revised pricing proposal did not adequately address all areas of concern with the proposed listing.
			Sponsor's comments:	The sponsor has no comment.
PRUCALOPRIDE, tablet, 1 mg and 2 mg (as succinate), Resotrans®	Treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate	Not currently PBS listed.		The PBAC rejected the submission on the basis of inadequate data to support the clinical benefit of prucalopride,

Janssen-Cilag Pty Ltd Minor submission	relief.			and an unworkable restriction likely to result in considerable leakage outside the intended population and the resultant high and uncertain costs to Government.
			Listing requested: <u>Restricted Benefit</u> The treatment of chronic functional constipation in adults meeting certain criteria.	See above.
			Comparator: Unchanged from July 2012. Best supportive care (stimulant laxatives in patients who have failed to achieve adequate relief with bulk forming agents, osmotic laxatives and stimulant laxatives).	See July 2012 outcome table.
			Clinical claim: Unchanged from July 2012. Prucalopride + best supportive care is superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo + best supportive care.	See July 2012 outcome table.
			Economic claim: Unchanged from July 2012. Cost-effectiveness compared to placebo + best supportive care.	See July 2012 outcome table.
			Sponsor's comments:	The sponsor has no comment.

RIVAROXABAN, tablets, 15 mg and 20 mg, Xarelto® Bayer Australia Ltd Major submission	Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.	<u>Authority Required (Streamlined)</u> Deep vein thrombosis <u>Authority Required (Streamlined)</u> Prevention of recurrent venous thromboembolism <u>Authority Required</u> Prevention of venous thromboembolism in a patient undergoing total hip replacement; Prevention of venous thromboembolism in a patient undergoing total knee replacement See www.pbs.gov.au for full restriction criteria.		The PBAC rejected the submission as it considered there to be no basis to support the claim of superior efficacy and safety of rivaroxaban over warfarin and hence considered the cost effectiveness analysis presented was not valid.
			Listing requested: <u>Authority Required (Streamlined)</u> Prevention of stroke or systemic embolism in an adult patient with non-valvular atrial fibrillation who meets certain criteria.	
			Comparator: Warfarin and aspirin	Given that the requested restriction was for patients inadequately controlled on warfarin or for whom warfarin is not suitable, the PBAC considered that aspirin was the more appropriate comparator. The PBAC noted, however, that aspirin is not the appropriate therapy for patients with a $CHADS_2$ score of greater than or equal to two and therefore the selection of the comparator might need to include consideration of different risk scores of different groups of patients. The PBAC considered that dabigatran may also be a relevant comparator.

			Clinical claim: Superior efficacy and safety versus warfarin and superior efficacy and equivalent safety compared with aspirin	As warfarin was not considered a relevant comparator for the group targeted in the proposed restriction, the PBAC was not able to interpret the submission's claim of superior efficacy and safety of rivaroxaban over warfarin. The PBAC considered that the claims that rivaroxaban is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over aspirin were not adequately supported by the data presented.
			Economic claim: Cost utility analysis versus warfarin and aspirin.	Not accepted. The PBAC considered that the economic analysis using the event rates from the ITT analysis for rivaroxaban and subgroup analysis rates from the below median TTR from the ROCKET trial was not appropriate. There were methodological and clinical issues which made it impossible to interpret the estimated ICER in the context of the proposed population for the PBS restriction.
			Sponsor's comments:	Bayer is disappointed with the outcome and will continue to work with the PBAC to make Xarelto available to patients with AF.

SORAFENIB, tablet, 200 mg (as tosylate), Nexavar® Bayer Australia Ltd Major submission	Treatment advanced hepatocellular carcinoma. Treatment of advanced renal cell carcinoma.	<u>Authority Required</u> Initial treatment, as the sole PBS-subsidised agent, of advanced (BCLC Stage C) hepatocellular carcinoma in a patient with a WHO performance status of 2 or less and Child Pugh class A <u>Authority Required</u> Continuing treatment, as the sole PBS-subsidised agent, of advanced hepatocellular carcinoma in a patient who has previously been treated with PBS-subsidised sorafenib and who does not have progressive disease See www.pbs.gov.au for NOTEs on the listing.		The PBAC rejected the submission on the basis that inadequate data was presented for use in the requested population
			Extend the current Authority Required listing to include the initial and continuing treatment of Stage IV clear cell renal carcinoma in a patient who has failed therapy with first line treatment and who meets certain criteria.	Appropriate, given that sunitinib and pazopanib are listed on the PBS as first-line treatment for renal cell carcinoma and that pivotal studies previously submitted did not support listing sorafenib in the first-line setting.
			Comparator: Placebo/best supportive care	Accepted.
			Clinical claim: Sorafenib is more effective than placebo but has worse toxicity compared to placebo.	Reasonable in the context of a patient population receiving cytokine therapy as first-line therapy but because sunitinib and pazopanib are now available on the PBS as first-line therapy, the PBAC did not accept the submission's clinical claim to be relevant in the context of the proposed listing.
			Economic claim: Cost-utility analysis compared to placebo/best supportive care.	Not accepted. The evidence base of the economic analysis was in patients who had predominantly received cytokine treatment as first-line therapy when the relevant therapies are now

				sunitinib and pazopanib. The PBAC therefore did not find the economic comparison to be valid or informative.
			Sponsor's comments:	The sponsor has no comment.
TAPENTADOL, tablets, 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 trial 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 on the basis of uncertain clinical need, potential high costs and the need for a full evaluation of equi-effective doses.
			Listing requested: <u>Restricted Benefit</u> Treatment of chronic severe disabling pain not responding to non-narcotic analgesics.	
			Comparator: Oxycodone controlled release (CR) as the main comparator and tramadol sustained release (SR) as the secondary comparator.	Accepted.
			Clinical claim: Tapentadol SR is equivalent in terms of comparative effectiveness and superior in terms of comparative safety (related to constipation and nausea/vomiting) to oxycodone CR. Tapentadol SR is non-inferior in terms of comparative effectiveness non-inferior in terms of comparative safety to tramadol SR.	The PBAC accepted (as previously) the clinical claim with respect to comparative effectiveness compared with oxycodone CR, however recalled it did not previously accept the claim of superior safety due to uncertainty in the data provided regarding constipation severity. The claim of non-inferiority in terms of comparative

				effectiveness and safety compared with tramadol SR was accepted. The PBAC again noted the many products for management of severe pain already listed on the PBS, and therefore continued to be unconvinced of a significant clinical need for tapentadol.
			Economic claim: Cost-minimisation to oxycodone CR. Cost-minimisation to tramadol SR.	The PBAC considered that the equi-effective analgesic doses (derived from the pooled analysis of the previous submissions' pivotal trials) and market share analysis (using BEACH data and PBS prescription data) required formal evaluation in the context of a major submission.
			Sponsor's comments:	CSL disagrees with the PBAC's recommendation, 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.