JULY 2007 PBAC OUTCOMES - "Subsequent" Decisions not to Recommend

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Etoricoxib tablets, 30 mg, 60 mg (Arcoxia®) Merck Sharp & Dohme (Australia) Pty Ltd Major submission	Symptomatic treatment of the signs and symptoms of osteoarthritis (OA). Treatment of acute gouty arthritis. Treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures. Currently, the 30 mg strength is not registered.	Not PBS listed.		The PBAC rejected the submission on the basis of uncertain comparative safety in terms of hypertension.
			<u>Restricted benefit</u> Symptomatic treatment of osteoarthritis.	Accepted
			Comparator: Celecoxib with lumiracoxib as a minor comparator.	Accepted
			Clinical claim: With respect to celecoxib, etoricoxib is: • equally efficacious • has similar GI tolerability • has similar CV tolerability • has similar hypertension tolerability. With respect to lumiracoxib, etoricoxib is: • equally efficacious • may have inferior GI tolerability • has similar CV tolerability • has similar hypertension tolerability.	Partially accepted. The comparison with celecoxib and lumiracoxib indicated that etoricoxib is no worse than these two comparators in terms of pain reduction. The PBAC accepted, on balance and particularly owing to the lack of a common reference traditional NSAID (tNSAID) as a comparator, that it is likely that etoricoxib is similar in GI safety compared with both celecoxib and lumiracoxib. Of greatest concern to the PBAC however, was the evidence that etoricoxib is more likely to increase blood pressure than celecoxib or lumiracoxib.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
			Economic claim: Cost-minimisation	Not accepted given the PBAC's conclusion about the clinical data.
			Sponsor's comments:	No comment.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Infliximab powder for IV infusion, 100 mg (Remicade®) Schering-Plough Pty Ltd Minor submission	Rheumatoid arthritis in adults. Ankylosing spondylitis. Crohn's disease. Refractory fistulising Crohn's disease. Psoriatic arthritis. Psoriasis. Ulcerative colitis.	<u>Section 100 public and private hospital authority required</u> Treatment of adult patients with severe active ankylosing spondylitis, who meet certain criteria; Treatment of adult patients with severe active rheumatoid arthritis, who meet certain criteria; Treatment of adult patients with severe active psoriatic arthritis, who meet certain criteria.		The PBAC was unable to reach a conclusion regarding the impact on the cost-effectiveness of treatment of the requested amendment to the PBS restriction, and the submission was rejected.
			Amend the Section 100 public and private hospital - authority required restriction for Crohn's disease in adults to allow patients to continue infliximab treatment following a reduction in CDAI score to less than or equal to 200, rather than to less than or equal to 150 as previously recommended.	Rejected
			Comparator: Not applicable	
			Clinical claim: Not applicable	
			Economic claim: Cost-effectiveness	Not accepted. The PBAC was concerned that, in the model presented, the incremental cost-effectiveness of infliximab appears insensitive to changes in either the severity of the disease at baseline or to the magnitude of the response.

			Sponsor's comments:	The sponsor is disappointed with the decision and is considering its position regarding any future course of action.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Methyl 5-amino-levulinate (MAL-PDT) topical cream, 160 mg/g, 2 g tube (Metvix®) Galderma Australia Pty Ltd Major submission	The treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable. Primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate. Treatment of biopsy-proven squamous cell carcinoma in situ (Bowen's disease), where surgery is considered inappropriate.	Not listed.		The PBAC rejected the submission because of uncertain comparative effectiveness and uncertain cost effectiveness.
			<u>Authority required</u> Treatment of superficial basal cell carcinoma (sBCC) in patients who cannot have surgical excision, cryotherapy, or curettage with diathermy.	Accepted, subject to the inclusion of "The date of the pathology report and name of the Approved Pathology Authority must be provided at the time of application" and "No applications for increased maximum quantities and/or repeats will be authorised".
			Comparator: imiquimod.	Accepted
			Clinical claim: MAL-PDT is no worse than imiquimod in terms of effectiveness and toxicity and exhibits at least equivalent or better safety profile and compliance rate.	Not accepted. The PBAC questioned whether the trials included patients who were representative of those for whom PBS listing was sought. Additionally, the only study with a direct comparison with imiquimod involved low numbers, and the resulting wide confidence intervals meant the PBAC considered that it was difficult to be confident about a conclusion that MAL-PDT is no worse than imiquimod in terms of safety and efficacy.

			Economic claim: Cost-minimisation	Not accepted. Given the uncertainty over the clinical comparison, the PBAC considered that the cost-minimisation approach was not justified on the basis of the evidence presented.
			Sponsor's comments:	The sponsor intends to work collaboratively with the PBAC to secure reimbursement of Metvix.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Pramipexole tablets, 125 microgram, 250 microgram (Sifrol®), Boehringer Ingelheim Pty Ltd Major submission	The treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa. The symptomatic treatment of idiopathic Restless Legs Syndrome.	Not PBS listed.		The PBAC rejected the submission as the evidence presented failed to support clinical superiority of pramiprexole over levodopa/benserazide and this resulted in uncertain cost-effectiveness.
			<u>Authority required</u> CAUTION: Episodes of sudden sleep without warning, during activity, have been reported with this drug. Initial treatment, by an appropriate medical specialist, of severe idiopathic Restless Legs Syndrome (RLS) in a patient who manifests all four diagnostic criteria below and who has a baseline International Restless Legs Syndrome Rating Scale (IRLS) score of greater than or equal to 21 points. -an urge to move the legs usually accompanied or caused by unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body	Accepted.

			parts are involved in addition to the legs); and -the urge to move or unpleasant sensations begins or worsens during periods of rest or inactivity such as lying or sitting; and -the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and -the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur during the evening or night. The baseline IRLS score must be included on the Authority form. Note: pramipexole is not PBS subsidised for Parkinson's disease nor restless legs syndrome secondary to other causes. First application for continuing treatment in a patient with severe idiopathic Restless Legs Syndrome (RLS) who has demonstrated a decrease in International Restless Legs Syndrome Rating Scale score of at least 30% from baseline. Second and subsequent applications for continuing treatment in a patient with severe idiopathic Restless Legs Syndrome (RLS) who has	

			previously been issued with an authority prescription for pramipexole.	
			Comparator: Levodopa/benserazide and placebo.	Accepted. The PBAC considered the comparison with levodopa/benserazide to be the more informative analysis.
			Clinical claim: Pramipexole has significant advantages in effectiveness over placebo and similar or less toxicity. Pramipexole has significant advantages in effectiveness over levodopa/benserazide and similar or less toxicity.	Not accepted. The PBAC noted that the evidence supported superiority of pramipexole over placebo in terms of effectiveness, but that it has greater toxicity, in particular nausea. The PBAC considered that the evidence presented to support the claim that pramipexole has a therapeutic advantage over levodopa/benserazide was weak. Overall, the PBAC agreed that the primary evidence supports that pramipexole is no worse than levodopa/benserazide, in terms of clinical effectiveness and toxicity, and does not justify the claim of superiority.
			Economic claim: Cost-effectiveness	Not accepted. The PBAC acknowledged the need for therapeutic options for Restless Legs Syndrome, but considered that the evidence presented failed to support superiority of pramipexole over levodopa/benserazide in terms of clinical effectiveness. This resulted

				in an uncertain cost-effectiveness ratio.
			Sponsor’s comments:	Boehringer Ingelheim does not wish to make any comments.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Sibutramine hydrochloride, capsules, 10 mg and 15 mg, (Reductil®) Abbott Australasia Minor submission	The management of obesity, including weight loss and maintenance of weight loss; should be used in conjunction with a reduced calorie diet.	Not PBS listed		The PBAC rejected the submission because of uncertainty about the extent of the clinical benefit and uncertain cost-effectiveness.
			<u>Authority required</u> For the treatment, in conjunction with a reduced caloric diet, of severe obesity (BMI $\geq$ 35 kg/m^2) in adults between 18 and 65 years of age who: -are normotensive patients with adequately controlled hypertension (< 145/90 mmHg) AND -have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) AND -have two or more of the following risk factors: Type 2 diabetes OR Triglycerides > 150 mg/dL (>1.695 mmol/L); OR HDL < 50 mg/dL (<1.295 mmol/L) for females or < 40 mg/dL (<1.036 mmol/L) for males. Alternative Option 1: Restrict to one 24 month period of therapy per lifetime.	The PBAC noted that the submission presented three options for the restriction but in the Pre-PBAC Response narrowed this to a modified restriction focusing on type 2 diabetics with severe obesity rather than on severely obese patients who are diabetic.

			Alternative Option 2: Restrict to obese diabetic patients only.	
			Comparator: Standard medical management	Accepted
			Clinical claim: Sibutramine has significant clinical advantages over the comparator. It is significantly more effective but has more toxicity.	Partially accepted. Although limiting continuous use to 24 months per lifetime mitigates some of PBAC's doubts about the extent and duration of clinical benefit, the effect of the weight loss achieved on clinically meaningful outcomes such as cardiovascular events is unknown. The PBAC also remained concerned, as in the previous submission, that the clinical importance of the treatment effects demonstrated on physiological variables need to be balanced against the potential for higher blood pressure, pulse rate and other adverse events associated with sibutramine.
			Economic claim: Cost-effectiveness	Not accepted. The PBAC considered some uncertainty remained about the results of the economic analysis as the model was unchanged from the previous submission.
			Sponsor's comments:	The sponsor acknowledges the PBAC's concerns and looks forward to addressing these issues with the aim of achieving successful reimbursement of sibutramine.

DRUG AND FORM	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR	PBAC OUTCOME AND COMMENTS
Teriparatide, solution for injection, in a 3 mL cartridge contained in a pre-filled disposable delivery device (pen), 250 micrograms in 1 mL, Forteo® Eli Lilly Australia Pty Ltd Major submission	Treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fracture. The maximal lifetime exposure to teriparatide for an individual patient is 18 months.	Not PBS listed		The PBAC rejected the submission because of uncertainty about the extent of clinical benefit over the comparator in the patient group for whom listing was sought and because the cost-effectiveness of treatment remains uncertain.
			<u>Authority required</u> Treatment by a specialist/consulting physician treating osteoporosis for postmenopausal women and men who have received at least 12 months continuous anti-resorptive therapy and have a very high risk of fracture. A very high risk of fracture is defined as: •The presence of two or more osteoporotic fractures where at least one incident fracture due to minimal trauma has occurred despite at least 12 months continuous therapy with an anti-resorptive agent of proven efficacy and safety for the treatment of osteoporosis; AND •A bone mineral density (BMD) T-score of -3.0 or less in a patient aged 70 years or older. The initial	The PBAC, although largely supportive of the intent of the sponsor's new restriction, was concerned that it may not be administrable due to difficulty in establishing whether any new (and often non-clinical vertebral) fracture occurred during or after the 12 months of continuous anti-resorptive treatment, without subjecting a large number of, often ultimately ineligible, patients to repeated X-ray examinations. The PBAC did not accept the proposed exclusion of patients younger than 70 years considering that this would exclude some patients at high fracture risk.

			authority application must state the date, site (femoral neck OR lumbar spine) and score of the qualifying BMD measurement. The radiological and/or laboratory reports and confirmation of the patient's prior treatment history supporting eligibility must be available for audit by Medicare Australia. Fracture must have been demonstrated radiologically and the year of plain x-ray, or CT-scan or MRI scan, and the year of DEXA must be included in the authority application. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body Anti-resorptive therapies for osteoporosis which will be accepted for the purposes of administering this restriction are alendronate sodium 10mg/day or 70mg QW, risedronate sodium 5mg/day or 35mg QW; raloxifene hydrochloride 60mg/day (women only); etidronate 200mg with calcium carbonite 1.25g/day; strontium ranelate 2g. If treatment with the above-mentioned drugs is	

			contraindicated according to the relevant TGA-approved Product Information, or intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use, the patient is exempted from the requirement to complete 12 months of therapy with that particular agent or class of agents. Details of the contraindication or intolerance must be provided at the time of application. Continuing treatment for osteoporosis in postmenopausal women and men with primary osteoporosis with two or more fractures due to minimal trauma and a bone mineral density T score of -3.0 or less where the patient has previously been issued with an authority prescription for this drug. Teriparatide is available with a lifetime maximum of 18 months teriparatide therapy (18 pens), a maximum of 18 pens will be reimbursed through the PBS.	
			Comparator: alendronate.	Accepted
			Clinical claim: Teriparatide is significantly more effective than the comparator, and can be considered either to have (i) more toxicity due to the possible	Not accepted. The Committee acknowledged that there is a trend in the data which suggests that teriparatide may be more effective than alendronate in preventing new

			implications of the preclinical finding of osteosarcoma, or (ii) less toxicity because of the time elapsed since marketing and precautions used.	vertebral and non-vertebral fractures, and that this has biological plausibility. However the results fail to reach statistical significance.
			Economic claim: Cost-effectiveness	Not accepted. The lack of a statistically significant difference in effectiveness together with doubts about the way the treatment benefit is modelled; the utility estimates used in the model; and the model's estimates of the relative risks of fracture following a previous fracture all contributed to Committee's uncertainty about the incremental cost-effectiveness of teriparatide.
			Sponsor's comments:	The sponsor disagrees with the decision and will consider the options available and refers you to its website (www.lilly.com.au) for further information.