**MARCH 2008 PBAC OUTCOMES - "Subsequent" Decisions not to Recommend**

| DRUG AND FORM | TGA INDICATION | CURRENT PBS LISTING | LISTING REQUESTED BY SPONSOR | PBAC OUTCOME AND COMMENTS |
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| DARBEPOETIN ALFA, injection, 200 micrograms in 0.4 mL pre-filled syringe, Aranesp®, 300 micrograms in 0.6 mL pre-filled injection pen and 500 micrograms in1 mL pre-filled injection pen, Aranesp SureClick®<br>Amgen Australia Pty Ltd<br><br>Minor submission | Darbepoetin alfa is indicated for the treatment of anaemia associated with chronic renal failure (CRF). Darbepoetin alfa is also indicated for the treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy. | Section 100 (Highly Specialised Drug) Private hospital authority required<br>Treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100g per L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia. | Section 100 (Highly Specialised Drug) Private hospital authority required.<br>Chemotherapy induced anaemia in patients with non-myeloid malignancy who satisfy all of the following criteria:<br>(1) Haemoglobin level of less than 100 g per L;<br>(2) At risk of requiring transfusion determined by clinical circumstances #<br>(3) Adequate iron stores defined by normal serum ferritin<br>(4) Cannot receive transfusion because of:<br>(a) religious beliefs; or<br>(b) the presence of at least one rare atypical or multiple typical preformed alloantibodies.<br><br># Clinical circumstances that increase the risk of transfusion include elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina or substantially reduced exercise capacity, energy or ability to carry out activities of daily living. | The PBAC considered the residual uncertainty about the net harm this drug could do to the population due to mortality increases from venous thromboembolic events (VTEs) (3% event rate reported) or the possible effect on tumour progression, remains unresolved.<br>The PBAC also took account of comment made at a recent meeting with patients and prescribers using erythopoeisis stimulating agents (ESAs), that consumers are concerned about the morbidity and mortality associated with their use in chemotherapy induced anaemia.<br>The PBAC therefore rejected the submission on the grounds of continuing uncertainty about whether the harms outweigh the benefits of treatment in the total patient group, and in the knowledge that where ESA use is considered essential for an individual patient access is available. |

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| | | | NOTE:<br>This drug is not PBS-subsidised for treatment of anaemia in cancer patients who are not receiving concurrent chemotherapy.<br>Haemoglobin concentration and rate of change should be monitored regularly during treatment with darbepoetin alfa and, if required, the dose should be adjusted or withheld according to the recommendations in the approved product information.<br>The haemoglobin concentration should aim to not exceed a target of 120g per L; the rate of haemoglobin increase should not exceed 10g per L in any 2-week period. | |
| | | | Sponsor's comments: | Although disagreeing with the recent recommendation, the Sponsor intends to work collaboratively with the PBAC to find a way to move forward with reimbursement of darbepoetin alfa for the treatment of chemotherapy-induces anaemia. |
| EXENATIDE pre-filled injection pens, 5 microgram and 10 microgam per dose, 60 doses, Byetta® Eli Lilly Australia Pty Limited | Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a | Not PBS listed | | As previously the Committee rejected the current application on the grounds of a high and uncertain cost-effectiveness ratio against the comparator, insulin glargine, in the absence of evidence of clinical benefit other than the observational |

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| Major submission | sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control. | | | finding of weight loss. |
| | | | Authority required<br>*Combination therapy with metformin and a sulfonylurea.*<br>Initiation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients who have an HbA1c greater than 7% despite maximally tolerated doses of metformin and a sulfonylurea.<br>The date of the HbA1c measurement, which must be no greater than 4 months old at the time of application, must be provided;<br>Continuation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients where the patient has previously been issued with an authority prescription for exenatide.<br><br>Authority required<br>*Combination therapy with metformin or a sulfonylurea*<br>Initiation of therapy, in combination with either metformin or a sulfonylurea, in type 2 diabetes mellitus patients who have an HbA1c greater than 7% and in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated.<br>The date of the HbA1c | Accepted subject to inclusion of a NOTE: Exenatide is not PBS-subsidised as monotherapy or in combination with insulins or a thiazolidinediones.<br>Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances:<br>(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies<br>and/or<br>(b) red cell transfusion within the previous 3 months.<br>Patients in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The date of measurement of the most recent blood glucose level, which must be no greater than 4 months old at the time of application, must be provided. |

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| | | | measurement, which must be no greater than 4 months old at the time of application, must be provided<br>Continuation of therapy, in combination with either metformin or a sulfonylurea, in type 2 diabetes mellitus patients where the patient has previously been issued with an authority prescription for exenatide. | |
| | | | Comparator: Insulin glargine as the main comparator, with rosiglitazone and insulin aspart as secondary comparators. | Accepted |
| | | | Clinical claim: Exenatide is equivalent to insulin glargine and rosiglitazone in terms of glycaemic control and safety, but superior in terms of weight management. | Partially accepted.<br><br>PBAC has accepted exenatide non-inferior to insulin glargine in terms of HbA1c, however the claim of non-inferiority to rosiglitazone has not been demonstrated.<br><br>PBAC considered exenatide associated with higher incidence of adverse events versus glargine. Insufficient data presented to assess comparative safety compared to rosiglitazone.<br><br>PBAC accepted statistically significant difference seen in weight changes with exenatide and insulin glargine in short term studies, but this benefit has not been shown to be durable in the longer term. |

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| | | | Economic claim:<br>Cost utility | Not accepted. The PBAC considered uncertainties around the clinical benefit result in uncertainty in the model outputs. Further, interpretation of model outputs were also marred by uncertainties in utlility values and a lack of clarity in the model. |
| | | | Sponsor's comments: | The sponsor needs to clarify the decision with the PBAC, but refers you to its own website for further information.<br>www.lilly.com.au |
| METHYL AMINOLEVULINATE cream 160 mg/g 2 g tube, Metvix®, Galderma Australia Pty Ltd<br><br>Major submission | Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable.<br>Primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate.<br>Treatment of biopsy-proven squamous cell carcinoma in situ (Bowen's disease), where surgery is considered inappropriate. | Not PBS listed | | The Committee rejected the application because of uncertain comparative effectiveness and additionally because of problems with the cost-minimisation analysis. |
| | | | <u>Authority Required</u><br>Treatment of superficial basal cell carcinoma (BCC) in patients who cannot have surgical excision, cryotherapy, or curettage with diathermy. The lesion must be previously untreated and the diagnosis confirmed by biopsy. The date of the pathology report and name of the Approved Pathology authority must be provided at the time of application. | Accepted, amended as follows:<br><u>Authority required</u><br>Treatment of biopsy confirmed primary (previously untreated with the sole exception of lesions treated with methyl aminolevulinate photodynamic therapy in the preceding 3 months) superficial basal cell carcinoma (sBCC) in a patiens for whom surgical excision, cryotherapy, or curettage with diathermy are inappropriate and topical drug therapy is required.<br>The date of the pathology report and name of the Approved |

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| | | | | Pathology Authority must be provided at the time of application.<br>NOTE:<br>No applications for increased maximum quantities and/or repeats will be authorised.<br>Treatment of recurrent (previously treated) lesions will not be authorised. |
| | | | Comparator: Imiquimod | Accepted |
| | | | Clinical claim: MAL-PDT is non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over imiquimod. | Not accepted. The PBAC noted no new data were presented to alter its view that non-inferiority to imiquimod in terms of safety and efficacy has not been demonstrated. |
| | | | Economic claim:<br>Cost-minimisation | Not accepted. The economic analysis was not acceptable give the clinical claim was not substantiated. Additionally there were concerns about some costs included in the analysis. |
| | | | Sponsor's comments: | The sponsor disagrees with the decision and will consider the options available and refers you to its website (www.treatskincancer.com or www.metvix.com) for further information. |
| PARICALCITOL, capsules,<br>1 microgram,<br>2 micrograms and<br>4 micrograms, | Paracalcitol is indicated for the treatment of the biochemical manifestations of secondary | Not PBS listed | | The PBAC rejected the application because of concerns about the validity of the clinical claim of superiority for paricalcitol over calcitriol and because of the |

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| Zemplar®, Abbott Australasia Pty Ltd<br><br>Major submission | hyperparathyroidism associated with chronic kidney disease | | | resulting uncertain cost-effectiveness. |
| | | | <u>Authority required</u><br>Treatment by a nephrologist of patients with end stage renal disease receiving dialysis who have secondary hyperparathyroidism (iPTH value > 300 pg/mL (30pmol/L) AND<br>(i) Phosphate >1.6mmol/L OR<br>(ii) Ca > 2.4 mmol/L<br><br>NB: Intact PTH should be monitored quarterly (measured at least 12 hours post dose) and the dose adjusted as necessary to maintain an appropriate iPTH level. | Partially accepted. PBAC considered some additional work may be needed to refine. |
| | | | Comparator: Oral calcitriol | Accepted |
| | | | Clinical claim: Paracalcitol has significant advantages in effectiveness over calcitriol. | Partially accepted. The PBAC accepted there is a mortality advantage for intravenous (IV) paracalcitol over IV calcitriol. However, uncertainty remained around the interpretation of hospitalisation data and applicability of IV findings to the oral formulation. Insufficient evidence was provided to allow a conclusion about comparative safety. |
| | | | Economic claim:<br>Cost-effectiveness | Not accepted. The PBAC was concerned at the approach to |

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| | | | | hospitalisation rates and also the uncertainties that flowed from the clinical issues above. |
| | | | Sponsor's comments: | The sponsor will continue to work with the PBAC to achieve a successful listing. |
| SIBUTRAMINE, capsules, 10 mg and 15 mg, Reductil® Abbott Australasia Pty Ltd<br><br>Major submission | Sibutramine is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. Sibutramine is recommended for obese patients with an initial body mass index greater than or equal to 30kg per square metre, or greater than or equal to 27kg per square metre in the presence of other obesity-related risk factors (e.g diabetes, dyslipidaemia, hypertension). Sibutramine may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) i.e | Not PBS Listed | | The PBAC rejected the application because although the current submission had achieved a greater focusing of the restriction and reduced the overall cost to the PBS, it had provided no further progress in terms of answering the PBAC's previous doubts about the extent of clinical benefit, and hence the resulting uncertain cost-effectiveness. |
| | | | <u>Authority required</u><br>For the treatment, in conjunction with a reduced caloric diet, of type 2 diabetic adults between 18 and 65 years of age with obesity (BMI ≥ 30 kg/m2) who:<br>• are normotensive patients with adequately controlled hypertension (< 145/90 mmHg) AND<br>• have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) AND<br>• have either:<br>1. Triglycerides > 150 mg/dL | The PBAC noted that in the sponsor's Pre-PBAC response it had agreed that only one course of initial treatment be authorised if recommended for listing. |

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| | patients who have difficulty achieving or maintaining greater than 5% weight loss within 3 months. BMI is calculated by taking the patient's weight, in kg, and dividing by the patients height, in metres, squared. Sibutramine is not intended for use in obese children under 18 years of age as safety and efficacy in this population has not been established. Sibutramine is not intended for use in elderly patients over 65 years of age as safety and efficacy in this population has not been established. | | (>1.695 mmol/L) OR<br>2.HDL < 50 mg/dL (<1.295 mmol/L) for females or < 40 mg/dL (<1.036 mmol/L) for males<br>• have an obesity management plan developed consistent with the Chronic Disease Management items on the Medicare Benefits Schedule.<br><br>Initial treatment:<br>Patients should receive an initial six months of treatment with Reductil. A weight review must be undertaken at six months and treatment must be discontinued for patients whose weight loss within six months after starting therapy has been less than 5% of their initial bodyweight. Patients are allowed to receive one course of initial treatment every 24 months.<br><br>Continued treatment:<br>Continuing treatment in patients who initially responded adequately to therapy as outlined above (i.e. a greater than 5% loss in weight after six months in diabetics). Total treatment will not exceed 24 months from initial application. | |
| | | | Comparator:<br>Lifestyle modification | Accepted |

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| | | | Clinical claim:<br>Sibutramine plus lifestyle modification has significant advantage in effectiveness over placebo plus lifestyle modification but has more toxicity. | Partially accepted. The PBAC accepted there was advantage for sibutramine (plus lifestyle modification) over placebo (plus lifestyle modification). However, this advantage needed to be balanced against findings of increased blood pressure and pulse pressure in the sibutramine group. Further, as previously, no direct data were submitted to indicate benefit for sibutramine in terms of cardiovascular outcome, or sustainability of weight loss. The PBAC noted the Sibutramine Cardiovascular Outcome Trial (SCOUT) was due to report in 2008. |
| | | | Economic claim:<br>Cost-utility analysis | The PBAC noted the major uncertainty with the analysis stems from the clinical issues ie the limitations of available data to reasonably predict long term weight changes. |
| | | | Sponsor's comments: | The sponsor will continue to work with the PBAC to achieve a successful listing. |
| SORAFENIB TOSYLATE, tablet, 200 mg, Nexavar® Bayer Health Care Bayer Schering Pharma | Sorafenib tosylate is indicated for the treatment of patients with advanced renal cell carcinoma | Not PBS listed | | The PBAC rejected the submission based on a high and uncertain cost effectiveness ratio. There is high clinical uncertainty associated with the claimed survival advantage and the place of sorafenib in the treatment algorithm is uncertain. |

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| Major submission | | | | |
| | | | <u>Authority required</u><br>Initial treatment of advanced (unresectable or metastatic) renal cell carcinoma in patients with WHO performance status 2 or less.<br>Continuing treatment of advanced renal cell carcinoma where the patient is not experiencing (or is free of) disease progression. Disease progression is defined as a 20% increase in the sum of the longest diameter of target lesions using X-ray, CT or MRI. | The PBAC considered the current evidence was in patients in whom cytokine therapy had failed, noting these therapies were not listed for use in advanced renal cell carcinoma. |
| | | | Comparator: Best supportive care (BSC) | Accepted |
| | | | Clinical claim: Sorafenib plus BSC is more effective than placebo plus BSC, and has greater toxicity | Not accepted. The PBAC considered the evidence in first line use showed no benefit in progression-free survival or overall survival. Further the extent of survival benefit in second line use was uncertain, despite significant progression-free survival in this trial. However, the clinical relevance of the gain had not been demonstrated as a surrogate to predict survival gain. |
| | | | Economic claim: cost utility analysis | Partially accepted. The PBAC considered the model sound, however, the cost-effectiveness ratio remained high, and uncertain |

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| | | | Sponsor’s comments: | The sponsor had no comment |