November 2006 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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| Bortezomib, vial, 3.5 mg, Velcade®, Janssen-Cilag Pty Ltd<br><br>Major submission | Treatment of multiple myeloma patients who have received at least one prior therapy and who have progressive disease. | Not PBS listed | | The PBAC rejected the submission because of unfavourable and uncertain cost effectiveness. |
| | | | Authority required for initial and continuing treatment of multiple myeloma in patients who have progressive disease with a WHO performance status of 2 or less, who have received at least one prior therapy and who have already undergone or are ineligible for a primary stem cell transplant and who are unsuitable for thalidomide or have treatment failure to a trial of at least 4 weeks of thalidomide at doses of at least 100 mg daily who meet certain criteria.<br>Disease status must be measured at baseline prior to commencing bortezomib, and repeated every 2 cycles by the same baseline measure up until cycle 6 or discontinuation. To ensure consistency in determining disease status, the same criteria used at baseline must be provided for repeated assessments and for all continuing treatment applications.<br>For eligibility for initial PBS-subsidised treatment with | The PBAC acknowledged the intention of the requested restriction to target use to a cost-effective population, reflected by the use of a continuation rule. However, despite the clinical need for treatments in this group of patients, PBAC considered the positioning of this drug in the treatment algorithm for multiple myeloma is not yet established. Thus, there were concerns about the practicality of such a complex restriction. |

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| | | | bortezomib, all patients must meet one or more of the following criteria measuring the extent of disease progression:<br>a)greater than 25% increase and an absolute increase of at least 5g/L in serum or urine M protein (monoclonal protein);<br>b)greater than 25% increase in 24-hour urinary light chain excretion, and an absolute increase of at least 200mg/24h; or<br>c)greater than 25% increase and an absolute increase in plasma cells in a bone marrow aspirate or on biopsy. absolute increase of at least 10%.<br>For patients whose disease cannot be measured by the disease progression criteria above or for patients with non-secretory multiple myeloma, one or more of the following criteria, in descending order of preference, may be provided:<br>d)development of hypercalcaemia (corrected serum calcium greater than 2.8 mmol/L not attributable to any other cause);<br>e)measurable increase in the size of existing lytic bone lesions or soft tissue plasmacytomas;<br>f) development of new bone lesions or soft tissue plasmacytomas (not including compression fracture); or<br>g)progressive renal failure due to multiple myeloma. | |
| | | | Comparator: mixture of salvage treatments, including autologous and allogeneic stem cell | As previously, the PBAC agreed that the use of a mixture of salvage treatments as an overall |

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| | | | transplant and a number of standard chemotherapy regimens as the main comparators. High dose dexamethasone (HDD) was used as a surrogate for all comparators in the main clinical and economic analyses presented in the submission. | comparator was appropriate. However, PBAC was uncertain about whether bortezomib would substitute for mini-allogeneic stem cell transplant and in what proportion of patients, in terms of cost offsets. |
| | | | Clinical claim: bortezomib is more effective than a mixture of salvage treatments including autologous and allogeneic stem cell transplant and standard chemotherapies, and has similar or less toxicity; bortezomib is more effective than HDD and has an equivalent but different toxicity profile. | Accepted. The PBAC noted there were no changes to the key trial data from the previous submission. |
| | | | Economic claim: Cost-effectiveness - cost utility approach. | Partially accepted. As previously, there were some uncertainties about the economic model. |
| | | | Sponsor's comments: | Janssen-Cilag has engaged in further discussions with the PBAC and clinicians to address issues raised by the Committee, with a view to ensuring access to bortezomib through the PBS. |

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| Docetaxel, vial 20mg and 80 mg, Taxotere®, Sanofi-Aventis Australia Pty Ltd<br><br>Major submission | Docetaxel is registered by the TGA for the following indications:<br>*Prostate cancer:*<br>Treatment of patients with androgen independent (hormone refractory) prostate cancer.<br>*Breast cancer:*<br>Treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed.<br>Taxotere in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.<br>Taxotere in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with node-positive breast cancer.<br>Taxotere is combination with trastuzumab is indicated for the treatment of metastatic breast cancer whose | Docetaxel is listed as an authority required benefit for the following:<br>Adjuvant treatment of node-positive breast cancer in combination with an anthracycline and cyclophosphamide.<br>Advanced breast cancer after failure of prior therapy which includes an anthracycline;<br>Advanced metastatic ovarian cancer after failure of prior therapy which includes a platinum compound;<br>Locally advanced or metastatic non-small cell lung cancer.<br>Treatment of HER-2 positive early breast cancer in combination with trastuzumab. | | The PBAC rejected the submission because of uncertain cost-effectiveness. |
| | | | Authority required listing for treatment of androgen independent (hormone refractory) prostate cancer. | The PBAC considered it may be appropriate to restrict treatment to patients with a Karnofsky's performance score of at least 60%, which is compatible with the trial data; and to 10 cycles, as it is rare for patients to tolerate more than six 3-weekly cycles of docetaxel. |
| | | | Comparator: Mitozantrone | Accepted |
| | | | Clinical claim: Docetaxel has significant advantages in effectiveness over the main comparator and is associated with similar or less toxicity. | Accepted. However, PBAC noted the survival gain was at the expense of the high toxicity of treatment with docetaxel. |
| | | | Economic claim:<br>Cost-effectiveness - cost utility approach. | Not accepted. PBAC considered the modelled economic analysis to be uncertain, particularly in relation to the utility values and the extrapolated survival benefit. |
| | | | Sponsor's comments: | Sanofi-aventis disagrees with the recommendation and is determined to ensure access to docetaxel for advanced prostate cancer patients. Further information can be found at www.sanofi-aventis.com.au |

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| | tumours overexpress HER-2 and who previously have not received chemotherapy for metastatic disease.<br>*Non-small cell lung cancer*: Treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum based chemotherapy.<br>*Ovarian cancer*: Treatment of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy. | | | |

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| Erlotinib, tablet, 25 mg, 100 mg and 150 mg, Tarceva®, Roche Products Pty Ltd<br><br>Major submission | Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. | Not PBS listed | | PBAC rejected the submission, mainly because of high and uncertain cost effectiveness ratios compared with BSC. There was also doubt about the claims for equi-effectiveness between erlotinib and docetaxel and erlotinib and pemetrexed. PBAC acknowledged that in some patients, particularly the frail elderly unable to tolerate more toxic therapies, an oral therapy for this disease could represent an advantage. |
| | | | Authority required for treatment as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a WHO status of 3 or less where disease progression has occurred following treatment with at least one chemotherapy agent. | Accepted |
| | | | Comparator: Best supportive care (BSC) as the comparator for patients who do not currently receive second or third line chemotherapy for locally advanced or metastatic NSCLC. Docetaxel and pemetrexed as the main comparators for patients currently receiving second or third line chemotherapy for locally advanced or metastatic NSCLC. | Accepted |
| | | | Clinical claim: Erlotinib is significantly more effective than BSC but has more toxicity in patients with previously-treated | The randomised trial of erlotinib versus BSC demonstrated statistically significant clinical benefits of erlotinib over BSC. |

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| | | | locally advanced or metastatic NSCLC.<br>Erlotinib has similar effectiveness to docetaxel, improved quality of life benefits and a more favourable toxicity profile.<br>Erlotinib has similar effectiveness to pemetrexed, and a different but no worse toxicity profile, in patients with previously treated locally advanced or metastatic NSCLC. | However, PBAC considered that a survival advantage for docetaxel over erlotinib could not be excluded. PBAC noted that the lack of a common reference in the comparison between erlotinib and pemetrexed restricted potential statistical analyses on any outcome measures to establish the relative effectiveness of erlotinib versus pemetrexed. |
| | | | Economic claim: Cost-effectiveness over BSC. Cost-consequence comparison with docetaxel. Cost-minimisation comparison with pemetrexed. | The principal concern of PBAC related to the cost-effectiveness comparing erlotinib with best supportive care. The costs per life year gained in the submission were considered high and uncertain. |
| | | | Sponsor's comments: | The sponsor will be considering its position regarding any future course of action. |

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| Sevelamer, tablet, 800 mg, Renagel®, Genzyme Australasia Pty Ltd<br><br>Major submission | Management of hyperphosphatemia in adult patients with stage 4 and 5 chronic kidney disease. | Not PBS listed | | PBAC rejected the submission because of uncertain clinical benefit and uncertain cost-effectiveness. |
| | | | *Option 1(preferred option)*<br>Authority required listing for treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis.<br>*Option 2*<br>Authority required listing for treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where:<br>(a)serum phosphate is greater than 1.6 mmol/L, or<br>(b)serum calcium x phosphate product is greater than 4.0 $mmol^2/L^2$.<br>*Option 3*<br>Authority required listing for treatment of hyperphosphataemia, in adult patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where:<br>(a)serum phosphate is greater than 1.6 mmol/L, or<br>(b)serum calcium x phosphate product is greater than 4.0 $mmol^2/L^2$,<br>and the patient is:<br>(a)aged ≥ 65 years, or | PBAC considered that the most restrictive of the proposed restrictions would be most likely to identify the population in whom treatment with sevelamer could be cost-effective. |

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| | | | (b)new to dialysis, or<br>(c)an Aboriginal or Torres Strait Islander person. | |
| | | | Comparator: Calcium carbonate | Accepted. |
| | | | Clinical claim: Sevelamer has significant clinical advantages over calcium carbonate and has similar or less toxicity. | PBAC considered that the pivotal uncertainties were whether the reduction in calcification reported in the supportive trials, the RIND Study and the Treat to Goal Study was an appropriate surrogate measure to predict mortality, and the extent of mortality benefit with sevelamer. PBAC concluded that although it was biologically plausible that reduction in calcification leads to a reduction in mortality, insufficient evidence had been provided in the submission to support the claim. |
| | | | Economic claim: Cost-effectiveness analysis | Given the uncertainty about the extent of mortality benefit, there was uncertainty about the results of the modelled economic analysis, which were sensitive to the estimates of incremental survival. |
| | | | Sponsor's comments: | Genzyme Australasia does not agree with the findings of the PBAC and is disappointed with the decision. Genzyme Australasia will continue to work with the PBAC to find a solution to listing sevelamer hydrochloride on the PBS. |

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| Sibutramine capsule, 10 mg and 15 mg, Reductil®, Abbott Australasia Pty Ltd<br><br>Major submission | 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 (BMI) greater than or equal to 30 kg per square metre or greater than or equal to 27 kg 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. 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. | Not PBS listed | | PBAC rejected the submission because of doubts about the extent and duration of clinical benefit, and the resulting uncertain cost-effectiveness. |
| | | | Authority required 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:<br>(a)are normotensive patients with adequately controlled hypertension (< 145/90 mmHg); AND<br>(b)have not adequately responded to an appropriate weight reducing regimen alone (hypocaloric diet and/or exercise); AND<br>(c)have 2 or more of the following risk factors:<br>(i)Type 2 diabetes; OR<br>(ii)Triglycerides > 150 mg/dL (> 1.695 mmol/L); OR<br>(iii)HDL < 50 mg/dL (< 1.295 mmol/L) for females or < 40 mg/dL<br>(<1.036 mmol/L) for males<br>Initial treatment in diabetic patients<br>Diabetic patients should receive an initial six months treatment with sibutramine. A weight review must be undertaken at 6 moths and treatment must be discontinued for diabetic patients | PBAC noted the intent of the restriction to provide access to the most severely affected patients. |

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| | 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.<br>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. | | 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 12 months.<br>Initial treatment in non-diabetic patients should receive an initial 3 months of treatment. A weight review must be undertaken at 3 months and treatment must be discontinued in non-diabetic patients whose weight loss within 3 months after starting therapy has been less than 5% of their initial bodyweight. Patients are allowed to receive one course of initial treatment every 12 months.<br>Continuing treatment in patients who initially responded adequately to therapy as outlined above (i.e. a greater than 5% loss in weight after 3 months in non-diabetics and after 6 months in diabetics). Total treatment will not exceed 24 months from initial application. | |
| | | | Comparator: Standard medical management, which consists of lifestyle modification; specifically a reduced calorie diet and/or exercise. | PBAC accepted standard medical management consisting of lifestyle modification (specifically, a reduced calorie diet and/or exercise) as the appropriate comparator noting that surgical interventions such as gastric banding is, in present day practice, a third line option after diet, exercise and pharmacotherapy have failed. |
| | | | Clinical claim: sibutramine has significant advantages in effectiveness over the comparator, but has more toxicity. | PBAC was concerned about whether a ≥5% weight loss, was a sufficient weight loss in the very obese population, as targeted in the |

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| | | | | requested restriction, particularly in the absence of evidence of long-term benefit. PBAC noted that systolic blood pressure, diastolic blood pressure and pulse rate were all statistically significantly higher in sibutramine-treated patients. |
| | | | Economic claim: Cost-effectiveness - cost utility approach. | PBAC considered that there were several problems relating to the construction of the modelled economic evaluation which relied on inputs not necessarily relevant to the treatment population targeted by the requested restriction, and this gave rise to uncertainties in the cost-effectiveness estimates. |
| | | | Sponsor's comments: | The Sponsor will be seeking advice from the PBAC to determine appropriate next steps. |

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| Somatropin (rbe), recombinant human growth hormone, injection, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg. 1.6 mg, 1.8 mg, 2 mg, 5 mg and 12 mg, Genotropin® , Pfizer Australia Pty Ltd<br><br>Major submission | Treatment of short stature due to decreased or failed secretion of pituitary growth hormone.<br>Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL.<br>Growth disturbances associated with gonadal dysgenesis (Turner's syndrome).<br>Improvement of body composition and treatment of short stature associated with Prader-Willi syndrome (PWS) in paediatric patients.<br>Treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age.<br>Chronic renal | Short stature in accordance with the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit'.<br><br>These guidelines may be obtained from the Department of Health and Ageing's internet site at http://www.health.gov.au/pbs/supply/hghguidelines.htm | | Although PBAC was sympathetic to this small patient group and acknowledged that some patients with PWS were receiving PBS subsidy for somatropin based on auxological criteria under the current Growth Hormone Program, it rejected the submission as the long-term benefit of treatment is uncertain resulting in uncertain cost-effectiveness. |
| | | | Section 100 Human Growth Hormone Program for the treatment of children with Prader-Willi Syndrome (PWS). | Accepted. However PBAC was concerned about ceasing treatment on reaching adulthood because data presented suggested that any benefit may be removed on the cessation of somatropin (Hoybye (2005)). |
| | | | Comparator: Placebo | Accepted |
| | | | Clinical claim: Treatment with growth hormone improves both linear height and body composition in PWS patients, irrespective of the relative height compared to no treatment, but may be associated with more toxicity. | PBAC noted that the percent body fat reduction was the most convincing evidence presented because the results reached statistical significance, but it was unclear how this reduction could be extrapolated to more patient relevant outcome measures. PBAC noted that data presented, relating to changes in BMI and energy expenditure were not statistically significant. |
| | | | Economic claim: Cost-effectiveness | In the absence of any modelled economic analysis it was not possible to translate the trial based incremental cost into a cost per relevant health outcome. |

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| | insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73m2. | | Sponsor’s comments: | No comment |