| **Drug Name, form(s), strength(s) and Sponsor** | **TGA Indication** | **Current PBS Listing** | **Listing requested by Sponsor / Purpose of Submission** | **PBAC Recommendation** |
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| AFLIBERCEPT, 2 mg/0.05 mL injection, 1 x 0.05 mL vial and 2 mg/0.05 mL injection, 1 x 0.05 mL syringe  Eylea®  Bayer Australia Ltd | Indicated in adults for treatment of:  - neovascular (wet) age-related macular degeneration (wet AMD)  and  - visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) | Subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD) |  | The PBAC rejected the submission on the basis of unacceptably high and likely underestimated cost-effectiveness for aflibercept compared with placebo, and on the basis of inadequate comparative data against compounded bevacizumab. |
| Listing Requested:  Re-submission to request Authority required General Schedule listing for the treatment of macular oedema following central retinal vein occlusion (CRVO). | The PBAC noted that the requested restriction remained unchanged from the July 2013 submission and includes a requirement that patients have confirmed central retinal thickening on optical coherence tomography (OCT) and that continuing treatment be guided by OCT. |
| Comparator:  Best supportive care in the absence of injected therapy | The PBAC considered that best supportive care in the absence of injected therapy was a relevant comparator and that the submitted sham-controlled trials provided relevant information for PBAC to compare aflibercept with best supportive care.  The PBAC considered that compounded bevacizumab was also a relevant comparator because evidence of its current use in patients who would be eligible for PBS-subsidised aflibercept means that prescribers would replace compounded bevacizumab in practice with aflibercept if the PBS subsidises aflibercept.  The PBAC noted Departmental advice that, if compounded bevacizumab were to be considered for PBS listing, its pricing for PBS purposes would most likely reflect the approach to pricing already applied to bevacizumab as an oncology medicine through the Efficient Chemotherapy Funding Program. |
| Clinical claim:  As in July 2013, the resubmission claimed that aflibercept has superior effectiveness with a similar safety profile compared to placebo, and non-inferior in terms of efficacy and safety compared to ranibizumab. | The PBAC accepted these claims in July 2013. The PBAC saw no reason to change its previous conclusions in its consideration of the resubmission. |
| Economic claim:  Cost-utility analysis compared to placebo. | The PBAC considered that an inherent issue in the model structure was the link between best corrected visual acuity (BCVA) of the affected eye (which forms the basis of the transition probabilities used) and utility values which are affected by the overall BCVA of the patient. The PBAC considered that this leads to a significant overestimate of the utility benefits of aflibercept, therefore the resulting incremental cost-effectiveness over placebo is highly favourable to aflibercept.  The PBAC considered that more extensive respecification of the base case would be needed to account for this structural issue given the paucity of data.  Notwithstanding the inherent issue with the model structure in relation to the utility consequences of unilateral blindness being overestimated in the economic model, the PBAC further considered that the lifetime time horizon of the model was not adequately justified given the lack of knowledge of the long-term treatment effect and the potential for recurrence of CRVO. |
| Sponsor’s comments: | Bayer is concerned that the PBAC considers a product that has not been approved, formulated or manufactured for use in eye disease in Australia as an appropriate comparator against a TGA approved treatment in the reimbursement assessment. |
| BEVACIZUMAB, 100 mg/4 mL injection, 1 x 4mL vial and 400 mg/16 mL injection, 1x16 mL vial  Avastin®  Roche Products Pty Limited | Indicated in the treatment of:  - metastatic colorectal cancer  - locally recurrent or metastatic breast cancer  - unresectable advanced, metastatic or recurrent, non-squamous non-small cell lung cancer  - advanced and/or metastatic renal cell carcinoma  - grade IV glioma  - epithelial ovarian, fallopian tube or primary peritoneal cancer | Metastatic colorectal cancer |  | The PBAC rejected the resubmission because it did not accept the re-modelling proposed by the applicant and therefore did not accept that the reduced rebate was justified in terms of cost-effectiveness. Accordingly, the PBAC rejected the ICERs generated by these modelling approaches, as unacceptably high. The PBAC therefore reiterated its November 2013 recommendation in relation to the appropriate base case of the economic model and the consequence for the pricing of bevacizumab for the proposed restriction. |
| Listing Requested: To request listing as a Section 100 (Efficient Funding of Chemotherapy Program) +/- STREAMLINED benefit for the first-line treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. | The PBAC noted that the applicant had agreed to the wording of the PBS restrictions, the maximum amount per dispensing (reflecting a 7.5 mg/kg dose) and the numbers of repeats (allowing a maximum of 18 cycles of bevacizumab) as suggested by the November 2013 PBAC meeting. |
| Comparator:  Doublet chemotherapy (as represented by carboplatin plus paclitaxel) alone | The PBAC had previously accepted doublet chemotherapy alone as the appropriate comparator. |
| Clinical claim:  As in November 2013, the submission claimed that bevacizumab is superior in terms of effectiveness, but inferior in terms of safety. | The PBAC again accepted the claims for bevacizumab as being superior in terms of effectiveness but inferior for safety, compared to doublet chemotherapy alone. However the PBAC considered that the modelling approaches taken in the original submission, the resubmission and the pre-PBAC response all overestimated the incremental overall survival gain and the incremental QALYs gained. |
| Economic claim:  Cost-effective analysis compared to doublet chemotherapy alone | The PBAC did not accept the ICERs of either the resubmission or the pre-PBAC response because the Committee rejected both of the modelling approaches used to estimate the incremental QALYs gained. The PBAC therefore reiterated its previous recommendation in relation to the appropriate base case of the economic model and the consequence for the pricing of bevacizumab for the proposed restriction. |
| Sponsor’s comments: | The sponsor will be considering its position with regard to any further course of action. |
| ERLOTINIB, 25 mg tablet, 30, 100 mg tablet, 30 and 150 mg tablet, 30  Tarceva®  Roche Products Pty Limited | Non-small cell lung cancer:  - first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.  - maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy.  Efficacy is influenced by tumour characteristics.  - treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.  The treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. | Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |  | The PBAC rejected the submission and recommended the deletion of the current last-line PBS restriction of erlotinib because of uncertain net clinical benefit and unacceptable cost-effectiveness. |
| Listing Requested:  To request that the current Authority Required General Schedule listing for patients with locally advanced or metastatic (stage IIIB or IV) epidermal growth factor (EGFR) wild-type or unknown non-small cell lung cancer (NSCLC) who have progressed on prior platinum therapy and have reached a point where further cytotoxic therapy is not an option, is retained. | The PBAC recalled that it had requested the submission in order to decide whether the evidence available supported the tighter last-line PBS restriction implemented following its out-of-session recommendation in late 2013 to list erlotinib in the PBS for patients with advanced NSCLC and an EGFR mutation without defining in which line of therapy it should be used. The PBAC accepted that the appropriate comparator was best supportive care (BSC) in the tighter last-line restriction. |
| Comparator:  Best supportive care (BSC) | The PBAC considered this to be appropriate. |
| Clinical claim:  The submission claimed that erlotinib is superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care for the PBS population. | The PBAC considered that the primary source of evidence presented (the BR.21 trial and various post hoc subgroup analyses) did not represent patients in modern day clinical practice and tended to overestimate the extent of benefit by failing to adequately exclude patients with EGFR mutation positive tumours. The PBAC considered that the estimated extent of benefit of erlotinib over BSC in BR.21, with a median PFS gain of 0.4 months, truncated mean PFS gain of 1.7 months, and overall survival gain of up to 2 months, was small. |
| Economic claim:  A cost-utility of erlotinib over BSC in three different patient populations, each of which accepts an improved overall survival with erlotinib:   * + BR.21 ITT population;   + BR.21 EGFR wild type or unknown; and   + BR.21 squamous patients. | The PBAC considered that the first two population groups in the model are not representative of the intended PBS population and so considered only the third analysis.  The PBAC considered that, even were it to accept the claimed extent of benefit from the clinical evidence presented, the most likely ICER at the current erlotinib price was unacceptably high. |
| Sponsor comments: | The sponsor disagrees with the PBAC’s recommendation. |
| FAMPRIDINE, 10 mg tablet: modified release  Fampyra®  Biogen Idec Australia Pty Ltd | Indicated for the symptomatic improvement of walking ability in adult patients with multiple sclerosis (MS). | Not currently PBS listed |  | The PBAC rejected the submission on the basis of inadequate evidence of comparative effectiveness based on clinically meaningful outcome measures. Therefore the cost-effectiveness of fampridine compared to placebo had not been established. |
|  |  |  | Listing Requested:  Authority Required listing for the treatment for the symptomatic improvement of walking ability of an ambulatory patient with clinically definite multiple sclerosis who meets certain criteria. | The PBAC noted that the proposed restriction had changed from the November 2012 submission. The requirement that the patient complete a timed 25-foot walk test (T25FW) had been replaced by use of the Expanded Disability Status Scale (EDSS) to demonstrate walking impairment as the requirement to qualify for trialling fampridine, as well as measurement using the 12-point Multiple Sclerosis Walking Scale (MSWS-12) to identify responders for continued treatment. The PBAC recalled that it considered that the T25FW would be extremely difficult to rely on for differentiating responders and non-responders and that the T25FW is not routinely used in clinical practice. The PBAC was not convinced that the use of these 2 new scales would significantly improve the reliability of the identification of responders and non-responders. |
|  |  |  | Comparator:  Placebo, as a proxy for best supportive care. | The PBAC recalled that it had previously accepted placebo as an appropriate comparator. |
|  |  |  | Clinical Claim:  The re-submission described fampridine as superior in terms of comparative effectiveness and inferior in terms of comparative safety compared to placebo. | The PBAC considered that the claim of inferior comparative safety was reasonable. With respect to comparative effectiveness, the PBAC considered the absolute treatment effect with fampridine is modest, and there is considerable doubt over whether it will be seen in practice. |
| Economic Claim:  Cost-utility analysis of fampridine compared to placebo. | The PBAC did not consider the submission’s estimate of the incremental cost per QALY gained to be reliable and that at the price proposed, the ICER is likely to be unacceptably high. |
| Sponsor’s comments: | Biogen Idec is disappointed with the rejection made by the PBAC, and are concerned that people living with multiple sclerosis who experience mobility dysfunction will not be able to receive Fampyra under the Pharmaceutical Benefits Scheme. We refer readers to our own web site for a more detailed commentary www.biogenidec.com.au |
| FOLLITROPIN ALFA AND LUTOPIN ALFA, follitropin alfa 150 units + lutropin alfa 75 units [1 vial] (&) inert substance dilent [1 vial], 1 pack  Pergoveris®  Merck Serono Australia Pty Ltd | Indicated for the stimulation of follicular development in women with severe luteinising hormone (LH) and follicle stimulating hormone (FSH) deficiency. In clinical trials, these patients were defined by an endogenous serum LH of less than 1.2 IU/L. | Not currently PBS listed |  | The PBAC rejected the submission to list follitropin alfa + lutropin alfa fixed does combination (FDC) on the Section 100 IVF/GIFT Programme. The PBAC considered that the submission had not established the comparative effectiveness and safety of the FDC to either follitropin alfa given alone or the components - follitropin alfa and lutropin alfa- given separately or other products containing human menopausal gonadotrophin. |
| Listing Requested:  Section 100 In Vitro Fertilisation / Gamete Intrafallopian Transfer (IVF/GIFT) Programme listing for the treatment of patients who are receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule and who have severe LH deficiency. |  |
| Comparator:  The submission nominated follitropin alfa, one component of the FDC product, as the main comparator.  The submission also considered human menopausal gonadotropin (hMG) as an additional but minor comparator. | The PBAC did not agree that the correct comparator was follitropin alfa. The PBAC considered that the comparator should include both FSH and LH. |
| Clinical claim:  The submission claimed that LH and FSH, when given concomitantly, were superior to FSH administered alone in women with LH deficiency. | The PBAC noted that this superiority claim related only to the surrogate endpoint of follicular stimulation (or overstimulation) rather than for pregnancy outcomes.  The PBAC considered that the comparative safety of follitropin alfa +lutropin alfa was a concern, particularly the risk of ovarian hyperstimulation syndrome (OHSS). |
| Economic claim:  The submission proposed that the cost of follitropin alfa + lutropin alfa FDC will be the same as the cost of rFSH alone, with the cost of the rLH component to be covered by the sponsor at no additional cost to Government.  A formal cost-minimisation analysis for the comparison between follitropin alfa + lutropin alfa FDC and its individual components administered concomitantly was not presented in the submission. | The PBAC considered that a cost-minimisation approach would be reasonable only when the efficacy and safety of follitropin alfa + lutropin alfa FDC are non-inferior to rFSH and rLH administered concomitantly in the population with severe LH deficiency. However, the submission did not present clinical data for this comparison.  The submission did not provide an economic evaluation for the comparison between follitropin alfa + lutropin alfa FDC and human menopausal gonadotropin (hMG). |
| Sponsor’s comments: | The sponsor needs to clarify the decision with the PBAC and is committed to pursue reimbursement of Pergoveris for women with severe LH deficiency. |
| LENALIDOMIDE, 5 mg capsule, 21, 10 mg capsule, 21, 15 mg capsule, 21 and 25 mg capsule, 21  Revlimid®  Celgene Pty Ltd | Lenalidomide was TGA registered on 20 December 2007 and is currently indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy, in combination with dexamethasone and for the treatment of patients with transfusion dependent anaemia due to low or intermediate 1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. | Section 100 – Highly Specialised Drugs Program  [Authority Required](javascript://)  Multiple myeloma  Treatment Phase: Initial PBS-subsidised treatment  Clinical criteria:  The condition must be confirmed by a histological diagnosis,  AND  The treatment must be as monotherapy; OR  The treatment must be in combination with dexamethasone,  AND  Patient must have progressive disease after at least one prior therapy,  AND  Patient must have undergone or be ineligible for a primary stem cell transplant,  AND  Patient must have experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease, ***OR***  ***Patient must have experienced treatment failure after a trial of at least three (3) weeks of bortezomib (or other protesome inhibitor) of at least 1.3 mg/m2 twice weekly or failed to achieve at least a minimal response after three (3) more weeks of bortezomib therapy (or other protesome inhibitor) for progressive disease.***  AND  Patient must not be receiving concomitant PBS-subsidised bortezomib ***(or other protesome inhibitor)***. |  | The PBAC rejected the submission on the basis of the absence of the relevant economic comparison of lenalidomide to re-treatment with bortezomib or treatment with thalidomide. |
| Listing Requested:  The minor resubmission sought to amend the current Section 100 (Highly Specialised Drugs Program) listing that requires prior treatment failure with thalidomide, to wording that requires prior treatment failure with thalidomide or bortezomib in patients with multiple myeloma (MM). | The PBAC considered that the proposed change to the restriction is currently not supported by the evidence. Whilst there may be valid clinical grounds for clinicians to be able to prescribe lenalidomide upon disease progression after initial therapy with bortezomib, or for disease refractory to first-line bortezomib therapy, an assessment of comparative cost-effectiveness with either bortezomib re-treatment or thalidomide treatment, as appropriate, had not yet been considered and accepted by the PBAC. |
| Comparator:  As a minor submission, the resubmission did not formally nominate a comparator for economic comparison. | The PBAC considered that a formal economic comparison should be presented for consideration in which bortezomib in the re-treatment setting is the comparator. Alternatively, a formal economic comparison in which thalidomide is the comparator could be considered. |
| Clinical claim:  Regardless of the number of prior therapies, the use of lenalidomide following bortezomib is associated with a response in a higher proportion of patients than those treated with thalidomide or those who received re‐treatment with bortezomib. Also, neurotoxic effects from both bortezomib and thalidomide would be reduced due to reduced exposure to these drugs. | The PBAC considered that there may be clinical grounds for clinicians to wish to prescribe lenalidomide following progression with the use of bortezomib. However, as presented in a minor submission, conclusions on the relevant comparisons of lenalidomide to re-treatment with bortezomib or to treatment with thalidomide were not possible. |
| Economic claim:  The minor resubmission maintained that cost effectiveness for lenalidomide has been previously established in relapsed/refractory disease and that cost effectiveness has also been established for use of lenalidomide post bortezomib by association when bortezomib was PBS listed for newly diagnosed multiple myeloma on a cost‐minimisation basis with thalidomide. | The PBAC considered that a formal economic comparison should be presented for consideration in which lenalidomide is compared to re-treatment with bortezomib, and/or with treatment with thalidomide, consistent with its previous consideration from March 2013. The PBAC recalled that in March 2013, a cost-effectiveness analysis comparing lenalidomide to thalidomide in the re-treatment setting was not presented and that such a comparison remains an option for the sponsor. |
| Sponsor’s comments: | The sponsor strongly agrees with the PBAC that there are valid clinical grounds for use of lenalidomide upon disease progression post initial therapy with bortezomib or for disease refractory to first line bortezomib.  The sponsor maintains that prior to PBS listing of bortezomib in the newly diagnosed multiple myeloma setting, cost-effectiveness for lenalidomide had been established for the wider multiple myeloma patient population with relapsed refractory disease. Furthermore, Celgene is not able to meet the PBAC’s request for comparative cost-effectiveness with either bortezomib re-treatment or thalidomide in relapsed or refractory multiple myeloma post bortezomib, due to the lack of availability of this specific data set.  Despite this, Celgene is committed to ensure that the barrier to patient access for lenalidomide in this setting, is removed. |