July 2014 PBAC OUTCOMES - "Subsequent" Decisions not to Recommend

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| **Drug Name, form(s), strength(s), Sponsor, Type of submission** | **TGA Indication** | **Current PBS Listing** | **Listing requested by Sponsor / Purpose of Submission** | **PBAC Recommendation** |
| ADALIMUMAB, 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges and 2 x 0.8 mL syringes, Humira®, AbbVie Pty LtdChange to listing.(Major submission) | Patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks for treatment to continue treatment beyond that time | Treatment of severe active rheumatoid arthritis, severe active psoriatic arthritis, active ankylosing spondylitis, severe refractory Crohn disease and severe chronic plaque psoriasis.Refer to [www.pbs.gov.au](http://www.pbs.gov.au) for full details | Authority required listing for the treatment of moderately to severely active ulcerative colitis. | The PBAC rejected the request to extend adalimumab’s indications to include the treatment of moderate to severe ulcerative colitis on the basis that an economic comparison comparing adalimumab to infliximab is the most relevant comparison and on the basis that the evidence presented did not conclusively establish non-inferiority of adalimumab to infliximab.  |
| Comparator: Best supportive care. | Not accepted. Infliximab (recommended for listing in March 2014 for ulcerative colitis) was considered to be the most relevant comparator.  |
| Clinical claim: Superior to placebo in patients with moderately to severely active ulcerative colitis in terms of comparative effectiveness and marginally worse in terms of comparative safety.  | Accepted. Adalimumab treatment appears to be associated with a real but modest incremental clinical benefit over placebo. With regards to comparative safety, adalimumab is marginally worse compared to placebo. On the basis of the meta-analyses of the direct comparison of the ULTRA I and II evidence presented by the submission, for every 100 patients treated with adalimumab in comparison to placebo, at week 8:* Approximately 8 additional patients would have clinical remission; and
* Approximately 14 additional patients would have clinical response.

On the basis of the ULTRA II evidence presented by the submission, for every 100 patients treated with adalimumab in comparison to placebo, at week 52:* Approximately 9 additional patients would have clinical remission;
* Approximately 12 additional patients would have clinical response;
* Approximately 2 additional patients would have had iron deficiency anaemia;
* Approximately 3 additional patients would have had gastroenteritis; and
* Approximately 8 additional patients would have had nasopharyngitis.

In the re-submission’s supplementary comparison of adalimumab to infliximab, the PBAC observed that the indirect comparison of adalimumab to infliximab indicated a trend of inferior efficacy for adalimumab across all outcomes. Although the indirect comparisons of the relative risks and odds ratios resulted in no statistically significant differences between the drugs, the credible intervals were large (e.g. for response at 8 weeks odds ratio 0.45; 95% Credible Interval: 0.11 to 1.74). Therefore, the PBAC was concerned that adalimumab may be inferior to infliximab in the treatment of moderate to severe ulcerative colitis despite considering adalimumab to have equivalent efficacy to infliximab in disease indications other than ulcerative colitis. |
| Economic claim:Cost-utility analysis against best supportive care.  | Not accepted. The PBAC noted that the estimated ICER in the re-submission was highly sensitive to the health state values applied in the model, the source of the health state costs used and the estimate of the efficacy of adalimumab beyond trial duration. The true ICER realised in practice is likely to be significantly greater than claimed in the re-submission.The PBAC noted the sponsor’s willingness to accept listing on a cost-minimisation basis against infliximab in its pre-PBAC response. As the PBAC was yet to accept a clinical claim of non-inferiority to infliximab, the PBAC was not prepared to recommend listing on a cost-minimisation basis against infliximab at this stage. |
| Sponsor’s comments: | The sponsor will be considering its position regarding any future course of action.  |
| MULTICOMPONENT MENINGOCOCCAL GROUP B VACCINE (4CMENB), 0.5 mL suspension for injection pre-filled syringe, Bexsero®Novartis Vaccines and Diagnostics Pty LtdNew listing(Major submission) | Active immunisation against invasive disease caused by *Neisseria meningitidis* group B strains.  | This vaccine is not listed on the National Immunisation program (NIP) or the PBS | Inclusion on the National Immunisation program for the prevention of meningococcal B disease in infants and adolescents. | The PBAC rejected the resubmission requesting listing of the 4CMenB vaccine on the National Immunisation Program (NIP) Schedule for the prevention of meningococcal B disease in infants and adolescents. The resubmission was rejected on the basis of a limited demonstration of, and multiple uncertainties in relation to, the clinical effectiveness of the vaccine against the disease when delivered in a vaccination program, as well as an unacceptably high and uncertain ICER, including when based on optimistic assumptions about the extent and duration of effect and herd immunity. The submission proposed a managed entry scheme (MES) comprising of studies to address the clinical uncertainties. The PBAC considered that, although important, the proposed MES was a secondary issue which only warranted further consideration if a price commensurate with an acceptable ICER is proposed to enable a recommendation to list on the NIP in the first place. |
| Comparator: No vaccination.  | Accepted: The PBAC agreed that the nominated comparator was appropriate, given that no vaccine against meningococcal B infection is currently available. |
| Clinical claim: The resubmission described 4CMenB as superior in terms of comparative effectiveness, with an acceptable tolerability profile in infants and adolescents.  | Not accepted: The PBAC noted that no direct evidence was presented regarding vaccine efficacy against infection and disease. The PBAC acknowledged the limitations in conducting randomised controlled trials measuring clinical outcomes for this vaccine due to the nature of the disease and the low number of total cases in Australia; however this lack of directly relevant data leads to multiple uncertainties in relation to the magnitude of clinical effectiveness against the disease.The PBAC reaffirmed its November 2013 conclusion that the vaccine is effective in inducing antibodies against the component antigens of 4CMenB. However, in the context of a population-based intervention against invasive meningococcal B disease (IMD), the Committee considered the clinical claim was highly uncertain because of the likely short persistence of the antibody response, uncertainty about the correlation between antibody responses and protection, the unknown effect on carriage of the bacteria, the overall uncertain long-term protective efficacy against infection and disease, and the unknown influence of projected herd immunity effects on overall disease burden.The PBAC reaffirmed its November 2013 conclusion that the rates of fever in infant participants of the trials receiving the vaccine would indicate that prophylactic paracetamol would be appropriate so that the local transient reactogenicity of 4CMenB would not be different to routine vaccination. However, the PBAC also noted that the impact of, and compliance with, this recommendation is unknown, and that a wider loss of confidence in the NIP may arise from concerns about increased rates of fever and convulsions. As suggested by ESC, the PBAC also noted that safety in adolescents appears acceptable.The PBAC noted that, on the basis of the results of the dynamic infectious disease model presented in the resubmission to translate serologic response reported in the trials:* approximately 336 IMD cases would be avoided over 5 years and approximately 10,532 individuals would need to be fully vaccinated to avoid one IMD case (over 5 years)
* approximately 13 deaths would be avoided over 5 years and approximately 272,224 individuals would need to be fully vaccinated to avoid one death (over 5 years).
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| Economic claim: Cost-utility analysis against no vaccination.  | Not accepted: The PBAC concluded that the re-submission’s base case ICER was unacceptably high and was based on uncertain and optimistic assumptions about the extent and duration of effect and herd immunity. The PBAC considered that before NIP listing could be reconsidered, there would have to be a proposal for a price that produces an acceptable ICER as a basis for a PBAC recommendation to list. |
| Sponsor’s comments: | The sponsor disagrees with the decision. The sponsor will be considering its position regarding any future course of action. |
| INGENOL, ingenol mebutate gel 0.15 mg/g (0.015%), 3 x 0.47 g, Picato® Leo Pharma Pty LtdNew listing(Minor submission) | Picato½ gel is indicated for the topical treatment of solar (actinic) keratoses in adults. | Ingenol is not currently PBS listed  | Restricted Benefit listing for treatment, as field therapy, of solar keratoses of the face and scalp. | The PBAC rejected the submission for PBS listing of ingenol for solar keratosis on the basis that the value of treating SKs was unknown.  |
| Comparator: The resubmission proposed best supportive care as the comparator.  | PBAC recalled that the resubmission in November 2013 nominated a ‘mixed comparator’ comprising three topical formulations (imiquimod, diclofenac 3% and 5-FU 5%) and ‘no treatment’, as the appropriate comparators. The PBAC considered imiquimod 5%, diclofenac 3% and 5-FU 5% were appropriate comparators for clinical purposes. The PBAC considered that “no treatment” was not an appropriate clinical comparator, noting that patients with solar keratosis were not likely to go untreated given that there are several treatment options available. However, the committee considered that this comparison was informative for estimating the cost-effectiveness of ingenol mebutate on the PBS, in the absence of any relevant PBS-listed comparators. In July 2014, the PBAC recognised that patients may prefer treatment with three days of ingenol compared to comparators such as 5-FU cream or cryotherapy, and that this preference could drive utilisation. |
| Clinical claim: No new clinical data were presented.  | In November 2013, the resubmission described ingenol mebutate as non-inferior to imiquimod 5% and 5‑FU 5% and superior to diclofenac 3% for complete clearance of solar keratoses. The PBAC considered these claims were reasonable, with the exception of the comparison versus 5-FU 5%. The resubmission described ingenol mebutate as non-inferior in terms of comparative safety over imiquimod 5%, diclofenac 3% and 5-FU 5%. The PBAC considered this claim to be reasonable. In July 2014, the PBAC recalled previous trial data (3 ingenol 0.015% (PEP005-015, PEP005-016, PEP005-025), plus 2 ingenol 0.05% trials (PEP005-014, PEP005-028) that demonstrated complete clearance of SK in 43% of ingenol treated patients compared to 4.3% in the placebo treated group. |
| Economic claim:Cost utility analysis was adopted.  | Not accepted. The economic model presented in this resubmission is the same model presented in the November 2013 submission without the offsets for the development and treatment of SCCs. The PBAC considered that the lack of demonstrable improvement in quality of life outcomes related to SK clearance remains a concern, despite new sensitivity analyses. The PBAC noted that the utility gain in the sensitivity analysis implies that a 70 year old patient would be willing to forgo 6 months of survival in a 10 year life expectancy (for the outcome of clearance of SK). The PBAC considered this to be implausible. |
| Sponsor’s comments: | The sponsor will be considering its position regarding any future course of action.  |