

PUBLIC SUMMARY DOCUMENT

Product: Adalimumab, 40mg/0.8mL injection, 0.8 mL cartridges and 0.8mL syringes, Humira[®]

Sponsor: AbbVie Pty Ltd.

Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission requested the inclusion of adalimumab on the PBS for the treatment of moderate to severe active ulcerative colitis.

2. Background

The PBAC had not previously considered listing of adalimumab for the treatment of moderate to severe active ulcerative colitis.

Adalimumab is currently listed on the PBS for the treatment of severe active rheumatoid arthritis, severe active psoriatic arthritis, juvenile idiopathic arthritis, active ankylosing spondylitis, complex refractory fistulising Crohn disease and severe chronic plaque psoriasis.

3. Registration Status

Adalimumab was TGA registered on 23 July 2013 for treatment of moderate to severe ulcerative colitis in adult patients who have had 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 of treatment to continue treatment beyond that time.

4. Listing Requested and PBAC's View

Authority required

Initial PBS-subsidised treatment with adalimumab by a gastroenterologist or a consultant physician of a patient 18 years or older who has:

- a. confirmed active ulcerative colitis
- b. moderate to severe ulcerative colitis (Full Mayo score of 6 to 12 points or Partial Mayo score of 4 to 9 points) despite concurrent treatment with systemic therapy; AND
- c. failed to achieve an adequate response, in intolerant or contraindicated to prior systemic therapy including:
 - I. a stable course of oral corticosteroid AND
 - II. immunosuppressive therapy including:
 - i. azathioprine, OR
 - ii. 6-mercaptopurine

Authority required

Continuing PBS-subsidised treatment with adalimumab by a gastroenterologist, a consultant physician or other consultant physician in consultation with a gastroenterologist, of a patient aged 18 years or older who has:

- a. demonstrated or sustained an adequate response to treatment with adalimumab.

An adequate response to adalimumab treatment is defined as:

- decrease in Partial Mayo score of greater than or equal to 2 points, OR
- decrease in Full Mayo score of greater than or equal to 3 points.

Listing was requested on a cost-effectiveness basis compared with standard care.

The PBAC agreed with the Drug Utilisation Sub-Committee (DUSC) that there may be use of adalimumab beyond the restriction in patients who achieve a partial response but do not meet the specified continuation criteria, with use of the partial Mayo score (which does not require endoscopy) rather than full Mayo score. The PBAC agreed with the Pre Sub-Committee Response (PSCR) (p4) that it is not appropriate to undertake a second endoscopy to determine response to adalimumab. The PBAC noted that the 2013 Gastroenterological Society of Australia Inflammatory Bowel Disease Clinical Update uses the Montreal classification to assess severity.

The PBAC also agreed with the DUSC that there is potential for patients to continue to trial adalimumab beyond 8 weeks even if response as defined in the continuation criteria are not met.

5. Clinical Place for the Proposed Therapy

Ulcerative colitis is one of two forms of idiopathic inflammatory bowel diseases. It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterised by inflammation and ulceration of the mucosal and submucosal intestinal layers. Ulcerative colitis is restricted to the colon and the rectum and microscopically, is restricted to the mucosa (epithelial lining of the gut). The clinical disease activity of ulcerative colitis is typically classified by activity (active or in remission), severity (mild, moderate and severe, or acute severe) and anatomic extent (distal or extensive).

The proposed treatment algorithm allows patients with moderate or severe active ulcerative colitis to receive biologic therapy (adalimumab or infliximab) when no longer responding to 5-aminosalicylic acid (5 ASA), corticosteroids and/or immunosuppressants. 'No longer responding' is defined as a patient with symptoms including frequent recurrences (with steroid treatment over two courses in one year, steroid dependence or refractory to steroids), or with contraindications and intolerance to current treatment. Patients with acute severe ulcerative colitis who respond to intravenous steroids or rescue therapy can receive biologic therapy if they respond to acute biologic therapy or if they have an acute response, but then have a non-response to standard maintenance therapy.

If recommended for listing, adalimumab would be the first biological agent PBS-subsidised for treatment of moderate to severe active ulcerative colitis.

6. Comparator

The submission nominated standard of care, including corticosteroids, 5-ASA and immunosuppressants, as the comparator. The PBAC accepted this as the appropriate comparator.

7. Clinical Trials

The submission presented one key trial M06-827 (52-week, induction and maintenance trial) and one supportive trial M06-826 (8-week induction study), both comparing adalimumab to placebo. The results of trial M06-827 were used in the economic model.

Trial M06-827 was a double-blind placebo-controlled trial of a period of up to 52 weeks where a total of 518 subjects were stratified by prior exposure to infliximab and/or other anti-TNF agents. In trial M06-827, 258 patients received adalimumab as follows: 160 mg at baseline; 80 mg at week 2, and 40 mg every week starting week 4. Two hundred and sixty patients received placebo at the same times. Following the 8-week induction period, patients who did not respond could be switched to open label adalimumab 40 mg every other week beginning of week 12. Patients who demonstrated inadequate response at two consecutive visits at least 14 days apart while on open-label adalimumab were permitted to increase the dose to 40 mg adalimumab weekly.

Trial M06-826 was a double-blind RCT followed by an open-label period. The protocol was amended four times. Under the original protocol or amendments 1 and 2, 186 patients were enrolled and randomised in a 1:1 ratio to receive adalimumab (160 mg, 80 mg, 40 mg, 40 mg at week 0, 2, 4 and 6) or placebo during the 12-week double-blinded induction period. At week 8, patients in the placebo arm crossed over and received 160 mg adalimumab and 80 mg at week 10. Patients in the treatment arm continued to receive 40 mg at week 8 and 10. From week 12 to week 52, all subjects received 40 mg of open-label adalimumab every other week.

Details of the trials are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
M06-827	<p>A Multicentre, Randomized, Double-blind, Placebo controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis.</p> <p>Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D'haens G, et al.. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis.</p> <p>Sandborn, WJ; Colombel, JF; D'Haens, G; Van Assche, G; Wolf, D; et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2.</p>	<p>March 2012</p> <p>Gastroenterology 2012;142: 257–265.</p> <p>Aliment Pharmacol Ther. 2013 Jan;37(2):204-13.</p>
M06-826	<p>A multicentre, randomised, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in patients with moderately to severely active ulcerative colitis</p> <p>Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial.</p>	<p>March 2012</p> <p>Gut 2011; 60:780-787.</p>

8. Results of Trials

With regard to comparative effectiveness, the PBAC considered that remission and response to treatment were clinically relevant outcomes for benefit. Trials M06-827 and M06-826 used change in full Mayo score as the primary and secondary outcome measure. The key results from trials M06-827 and M06-826 are presented in the table below.

Results of proportion of patients in remission and in response across the direct randomised trials

Trial ID	Adalimumab	PBO	ARD (95%CI)	RR (95%CI)	NNT ^b (95% CI)
Remission (Mayo score ≤2 and no individual subscore >1)					
At week 8					
M06-827	41/248 (16.5%)	23/246 (9.3%)	7.2 (1.3; 13.1)	1.8 (1.1; 2.9)	14 (8, 77)
M06-826 (A3)	24/130 (18.5%)	12/130(9.2%)	9.2 (0.9; 17.6)	2.0 (1.0; 3.8)	11 (6; 111)
M06-826 (E)	35/223 (15.7%)	16/222 (7.2%)	8.5 (2.6; 14.4)	2.2 (1.2; 3.8)	12 (7, 38)
Meta-analysis (I ² = 0%) ^a			8.2 (3.0; 13.0)	1.9 (1.3; 2.7)	12 (8, 33)
At week 52					
M06-827	43/248 (17.3%)	21/246 (8.5%)	8.8 (2.9; 14.7)	2.0 (1.2; 3.3)	11 (7, 34)
Sustained (both week 8 and 52)					
M06-827	21/248 (8.5%)	10/246 (4.1%)	4.4 (0.1; 8.7)	2.1 (1.0; 4.3)	23 (11, 1000)
Responder (Mayo score decrease ≥3 points; ≥30% decrease from baseline, decrease in RBS ≥1 or absolute RBS of 0 or 1)					
At week 8					
M06-827	125/248 (50.4%)	85/246 (34.6%)	16.0 (7.0; 24.0)	1.5 (1.2; 1.8)	6 (4, 14)
M06-826 (A3)	71/130 (54.6%)	58/130 (44.6%)	10.0(-2.1;22.1)	1.2 (1.0; 1.6)	10 (NE)
M06-826 (E)	116/223 (52.0%)	95/222 (42.8%)	9.2 (0.0; 18.5)	1.2 (1.0; 1.5)	11 (NE)
Meta-analysis (I ² = 11%) ^a			13.9 (7.0; 21.0)	1.4 (1.2; 1.6)	7 (5; 15)
At week 52					
M06-827	75/248 (30.2%)	45/246 (18.3%)	11.9 (4.5; 19.4)	1.7 (1.2; 2.3)	8 (5, 22)
Sustained (both week 8 and 52)					
M06-827	59/248 (23.8%)	30/246 (12.2%)	11.6 (4.9; 18.3)	2.0 (1.3; 2.9)	9 (5, 20)

A3 = all randomised and treated subjects enrolled after protocol amendments 3; E = all subjects who received long term adalimumab regardless of randomisation group and amendment; CI = confidence interval; PBO = placebo; ARD = absolute risk difference; RR = relative risk; NNT = number needed to treat; RBS = rectal bleeding subscore; **bold** = statistically significant.

^a The results of the meta-analysis is based on the data from trials M06-827 and M06-826 (ITT-A3).

^b Calculated during evaluation.

The PBAC noted that at week 8, there was a statistically significantly higher remission rate in the adalimumab group compared to placebo. The difference in remission rate at week 52 and the sustained remission rate were also statistically significant in trial M06-827. The PBAC also noted that the results showed a higher response rate for the treatment arm compared to placebo in both trials at week 8. At week 52 in trial M06-827, there were a higher proportion of responders in the treatment arm compared to placebo.

The PBAC considered that adalimumab treatment was associated with a real but modest clinical benefit, noting that approximately 50% of patients treated with adalimumab respond (at week 8), while less than 20% achieve remission.

With regard to comparative harms, in trial M06-827, there was a higher proportion (although not statistically significantly different) of patients with adverse events, serious adverse events, and adverse events leading to discontinuation in the placebo group than in the adalimumab group. The most common adverse events reported in trial M06-827 were gastrointestinal disorders and infections and infestations.

Events with a statistically significant difference between treatment arms were iron deficiency anaemia (2.7% in adalimumab vs. 0.4% in placebo arm), gastroenteritis (3.5% in adalimumab vs. 0.8% in placebo), nasopharyngitis (17.5% in adalimumab vs. 10.4% in placebo), injection site reaction related (12.1% in adalimumab vs. 3.8% in placebo) and hematologic related (1.9% in adalimumab vs. 0% in placebo).

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The reported adverse events were similar to those reported in the trials.

Overall, the PBAC considered the comparative harms of adalimumab were known and no new safety signals were observed in the trials and additional safety data presented in the submission.

A summary of the comparative benefits and harms for adalimumab versus placebo is presented in the table below.

Benefit/harms summary

Outcome	Number of participants (M06-827)	RR (95%CI)	Placebo arm event rate per 100 patients	Adalimumab arm event rate per 100 patients	RD (95% CI)
Benefits					
Remission (Mayo score ≤ 2 and no individual subscore >1)					
Week 8	494	1.8 (1.1; 2.9)	9.3	16.5	7.2 (1.3; 13.1)
Week 52	494	2.0 (1.2; 3.3)	8.5	17.3	8.8 (2.9; 14.7)
Sustained	494	2.1 (1.0; 4.3)	4.1	8.5	4.4 (0.1; 8.7)
Responder (Mayo score decrease ≥ 3 points; $\geq 30\%$ decrease from baseline, decrease in RBS ≥ 1 or absolute RBS of 0 or 1)					
Week 8	494	1.5 (1.2; 1.8)	34.6	50.4	16.0 (7.0; 24.0)
Week 52	494	1.7 (1.2; 2.3)	18.3	30.2	11.9 (4.5; 19.4)
Sustained	494	2.0 (1.3; 2.9)	12.2	23.8	11.6 (4.9; 18.3)
Harms					
Iron deficiency	517	6.9 (0.9; 55.8)	0.4	2.7	2.3 (0.2; 4.5)
Gastrointestinal	517	4.4 (1.0; 20.4)	0.8	3.5	2.7 (0.2; 5.2)
Nasopharyngitis	517	1.6 (1.1; 2.6)	10.4	17.5	7.1 (1.2; 13.1)

The PBAC considered that, based on these trials, for every 100 patients treated with adalimumab compared to placebo;

- Approximately 7 patients would have a remission at 8 weeks;
- Approximately 4 patients would have a sustained remission (both week 8 and 52);
- Approximately 16 patients would have responded at 8 weeks;
- Approximately 12 patients would have a sustained response (both week 8 and 52);
- Approximately 2 patients would experience iron deficiency anaemia;
- Approximately 3 patients would experience gastroenteritis; and
- Approximately 7 patients would experience nasopharyngitis.

9. Clinical Claim

The submission described adalimumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

The PBAC accepted that the claim of superior comparative efficacy was reasonable, but noted that the applicability of the claim to the requested PBS population was uncertain for the following reasons:

- The dose regimen and the continuation rule in trial M06-827 is different from those proposed in the PBS restriction;
- Dose escalation was allowed in trial M06-827 to 40 mg weekly.

The PBAC noted the sponsor's advice in its pre-PBAC response that it requested a PBS listing restricted to every other week dosing, and a sponsor supported compassionate supply process would apply for the small number of patients requiring dose escalation.

The PBAC considered the submission's claim that adalimumab was equivalent in terms of comparative safety to placebo was uncertain, noting the statistically significant differences in the incidence of the above mentioned adverse events compared with placebo.

10. Economic Analysis

The submission presented a cost-utility analysis. The economic model was a Markov model with two alternative treatment pathways (adalimumab + best supportive care (BSC) and placebo + BSC), three treatment status groups ('on assigned treatment', 'on BSC only following discontinuation of assigned therapy', and 'off medical treatment following surgery') and eight mutually exclusive health states that compared adalimumab (added to standard care) to standard care alone over a 20-year duration. Utility values were derived from a study by Tsai et al (2008). The economic evaluation produced an incremental cost per quality adjusted life year (QALY) in the range \$15,000-\$45,000.

The PBAC agreed with the Economic Sub-Committee (ESC) that the structure of the economic model was not appropriate for the following reasons:

- The proportions of patients on adalimumab, best supportive care, and no treatment are not linked to the eight health states in the economic model.
- In subsequent cycles a large proportion of patients with a response or remission are not being treated with adalimumab or placebo.
- The cost of adalimumab treatment or best supportive care is not associated to each of the health states. Instead, each health state only accounts for the cost of other healthcare resource utilisation, while the adalimumab costs are linked to adalimumab treatment.

The PBAC also noted that the model did not include treatment discontinuations.

The PBAC noted the sensitivity analyses performed during the ESC evaluation where the model structure was changed so that the costs of treatment were linked to the health states:

- The proportion of patients receiving treatment includes all patients in remission and response states;
- Patients in the non-response state receive BSC;

- Patients not receiving treatment are patients in the post-surgery with complication, post-surgery no complications, surgery and death states.

Additionally, the following changes to the model input parameters were made:

- Use of partial Mayo score rather than the full Mayo score;
- Use of utility values from Saini (2012).

The loss of remission and loss of response were re-estimated using the sustained remission and sustained response outcomes at week 52.

The additional sensitivity analyses produced ICERs in the range of \$45,000-75,000 per QALY (sensitivity analyses around input parameters) and in the range of \$105,000-200,000 per QALY (structural sensitivity analysis and multivariate analysis).

The PBAC noted the revised ICERs and sensitivity analyses presented in the sponsor's PSCR were in the range of \$45,000 and 75,000 per QALY.

The PBAC noted that the revised ICER presented in the PSCR was substantially higher than the base case ICER presented in the submission. The PBAC noted that the economic model maintained continued response beyond the trial duration, while patients are not being treated. The PBAC considered this to be neither justified nor realistic. The PBAC also noted that the model was also highly sensitive to efficacy (sustained response, 95% CI of efficacy, partial versus full Mayo score), utility values and health care resource use.

The PBAC noted the offer by the sponsor in its pre-PBAC response, which reduced the revised base case ICER presented in the PSCR, while remaining in the range of \$45,000 - 75,000 per QALY.

Overall, the PBAC considered the economic analysis to be highly uncertain, with most of the issues identified likely to favour adalimumab. The PBAC considered that the economic modelling was not able to provide a reliable estimate of the cost-effectiveness of adalimumab.

11. Estimated PBS Usage and Financial Implications

The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of adalimumab for moderately to severely active ulcerative colitis.

The submission estimated a net cost per year to the PBS / RPBS of \$30-60 million in Year 5 of listing.

The PBAC agreed with the DUSC that the estimates presented in the submission were uncertain for the following reasons:

- The estimated size of the eligible population relied heavily on a small clinician survey;
- The submission did not provide sufficient rationale for the extent and rate of uptake presented;
- The compliance rate of 100% is too high for an injectable medicine. Patients may also take a treatment break if they develop an infection;

- There may be use of adalimumab beyond the restriction in patients who achieve a partial response but do not meet the continuation criteria.

12. Recommendation and Reasons

The PBAC rejected the submission on the grounds that the cost-effectiveness of adalimumab was not able to be estimated by the economic analysis presented in the submission. The PBAC also considered the requested listing to have a high and uncertain total cost for the modest clinical benefit observed in the trials presented.

The PBAC considered the economic analysis to be highly uncertain, with most of the issues identified likely to favour adalimumab. The PBAC considered that the economic modelling did not provide a basis for the Committee to be satisfied that the cost-effectiveness of adalimumab could be established. The PBAC recommended that the model in any future major submission should account for treatment discontinuations and link health states to the cost of treatment.

The PBAC acknowledged there is a place for adalimumab in the treatment of moderate to severe active ulcerative colitis. The PBAC noted and welcomed the input received from individuals (63), healthcare professionals (8) and organisations (1) in support of the submission. The perceived benefits of treatment included efficacy, avoiding surgery and associated disfigurement, and ability to return to work/ caring role. The input also highlighted access issues as being important to patients and prescribers.

The PBAC agreed that standard care, including corticosteroids, 5-ASA and immunosuppressants, was the appropriate comparator.

Based on the trial data presented in the submission, the PBAC considered that adalimumab treatment was associated with a real but modest clinical benefit, noting that approximately 50% of patients treated with adalimumab respond (at week 8), compared to 35% treated with placebo, while less than 20% achieve remission.

The PBAC accepted that the submission's claim of superior comparative efficacy compared to placebo was reasonable, but noted that the applicability of the claim to the requested PBS population was uncertain for the reasons described above. The PBAC considered the submission's claim that adalimumab was equivalent in terms of comparative safety to placebo was uncertain, noting the statistically significant differences in the incidence of the above mentioned adverse events compared with placebo.

The PBAC noted that the submission's estimate of net cost per year to the (R)PBS was greater than \$20 million per year in each of the first five years of listing. The PBAC considered this to be high in relation the clinical benefit associated with treatment. The PBAC also considered the submission's estimates of utilisation and cost to be uncertain for the reasons identified by the DUSC.

The PBAC noted that the submission meets the criteria for an Independent Review.

Outcome:

Rejected

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

AbbVie submitted Humira for the treatment of chronic refractory moderate to severe ulcerative colitis to address the high clinical need for pharmacological treatment options for this patient population. AbbVie is disappointed with the PBAC outcome and are working with the PBAC to understand the issues raised.