PUBLIC SUMMARY DOCUMENT
Product: ADALIMUMAB, 40 mg in 0.8 mL pre-filled syringe, packs of 2 and 6, Humira®, ADALIMUMAB PEN, 40 mg solution in 0.8 mL pre-filled pen, packs of 2 and 6, Humira Pen®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought an extension to the current PBS-listed indications to include treatment of patients with moderate to severe Crohn disease (Crohn Disease Severity Index (CDAI) $\geq$ 300) or in certain post-surgical Crohn patients. The submission also requested the PBAC consider the addition of a grandfather clause to the requested restriction for adalimumab for Crohn disease to allow patients who enrolled in the original adalimumab clinical trial for Crohn disease access to PBS-subsidised treatment.

2. Background

Adalimumab is currently listed on the PBS for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis and has not previously been considered for the treatment of Crohn disease.

3. Registration Status

Adalimumab is TGA approved for, among other uses, the treatment of moderate to severe Crohn disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab.

4. Listing Requested and PBAC's View

The submission proposed two listing alternatives.

In both alternatives, access to initial PBS-subsidised treatment is limited to adults who:

1) Have a diagnosis of Crohn disease confirmed by endoscopy or radiologic evaluation and:
   (i) Severe Crohn disease (Crohn Disease Activity Index $\geq$ 300) or
   (ii) Patients with an ileostomy or colectomy and
2) Where conventional therapy has failed, including corticosteroids and immunomodulator (azathioprine/6-MP &/or methotrexate) or where the patient is unable to use immunomodulator therapy because of side-effects.

Continuing treatment in alternative (1) is proposed to be limited to those patients who have achieved remission (CDAI $\leq$ 150) on initial treatment. In Alternative (2), the first application for continuing treatment would be approved if the patient had achieved a decrease in CDAI score of $\geq$ 150 points, with subsequent approvals for continuing treatment requiring the achievement of remission (CDAI $\leq$ 150).

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Adalimumab would provide clinicians with an alternative PBS-subsidised treatment to infliximab for Crohn patients who continue to have active disease despite optimal treatment with conventional therapies.

6. Comparator

The PBAC agreed that infliximab is the relevant comparator.

7. Clinical Trials

The submission presented 7 randomised, placebo controlled, double-blinded multi-centre studies including:

- CLASSIC I (M02-403), a study of the human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with Crohn Disease 2006;
- CHARM (M02-404), a study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn Disease 2006;
- CLASSIC II (M02-433), a study of the human anti-TNF monoclonal antibody adalimumab for the maintenance of clinical remission in subjects with Crohn Disease 2006;
- GAIN (M04-691), a study of the human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with moderate to severe Crohn Disease who have lost response or are intolerant to infliximab 2006;
- ACCENT I, Maintenance infliximab for Crohn disease; Rutgeerts (1999), Efficacy and safety of retreatment with anti-tumour necrosis factor antibody (infliximab) to maintain remission in Crohn disease;
- Targan (1997), a short term study of chimeric monoclinal antibody cA2 to tumour necrosis factor α for Crohn disease.
- Rutgeerts et al. (1999), a multi-centre, randomised, double-blind, placebo-controlled extension study of Targan et al. (1997) comparing infliximab 10mg/kg or placebo every 8 weeks for maintenance of clinical response over 48 weeks.

These trials had been published at the time of submission are as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Adalimumab		
CLASSIC I (M02-403)/ Hanauer SB,	A multi-center, randomized, double-blind, placebo controlled study of the human anti-TNF monoclonal antibody Adalimumab for the induction of clinical remission in subjects with Crohn Disease. 2006.	2006 Gastroenterology; 130(2): 323-333.
CHARM (M02-404)/ Colombel J-F	A multi-center, randomized, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn disease. 2006.,	2007 Gastroenterology; 132(1): 52-65.
CLASSIC II (M02-433)/ Sandborn WJ	A multi-center, randomized, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the maintenance of clinical remission in subjects with Crohn disease. 2006.	2007 Gut; (epub: 13/02/2007).
GAIN (M04-691)/	A multi-center, randomized, double-blind, placebo controlled study of the human anti-TNF monoclonal	2007 Annals of Internal

Sandborn WJ	antibody adalimumab for the induction of clinical remission in subjects with moderate to severe Crohn disease who have lost response or are intolerant to infliximab. 2006.	Medicine; (epub: 30/04/2007).
Infliximab		
ACCENT-I/ Hanauer SB,	Maintenance infliximab for Crohn disease: the ACCENT I randomised trial.	2002 The Lancet; 359:1541-1549.
ACCENT-II/ Sands BE	Infliximab maintenance therapy for fistulizing Crohn disease.	2004 New England Journal of Medicine; 350:876–885.
Rutgeerts et al. (1999)	Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn disease.	1999 Gastroenterology; 117(4): 761-9.
Targan et al.	A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor α for Crohn disease.	1997 New England Journal of Medicine; 337:1029-1035.

The comparative efficacy of adalimumab and infliximab induction was derived directly from presented results in CLASSIC-I (160/80mg every other week (eow)) and ACCENT-I (5mg/kg every 8 weeks only). Comparison of maintenance dosing was derived directly from results from initial (induction) responders in CHARM (40mg eow) and ACCENT-I (5mg/kg), which was the focus of the submission. However, the PBAC considered the comparison of CLASSIC-II and ACCENT-I is also informative, particularly given that CHARM administered an induction dose regimen lower than the regimen proposed for PBS listing.

8. Results of Trials

The results of key studies are summarised below.

Proportion of patients in remission (CDAI<150) at week 26 and 56 in CHARM (mITT and ITT population) and week 24 and 26 in CLASSIC-II (double-blind treatment groups)

Trial ID AD dose	AD n/N (%)	Placebo n/N (%)	Risk difference [95%CI]	p-value	Relative Risk [95%CI]	p-value
CHARM mITT and ITT population						
mITT population [a]						
Week 26						
40mg eow (all) 40mg eow(300) 40mg ew	68/172 (40) 34/95 (36) 73/157 (47)	29/170 (17) 12/95 (13)	22.5 [13.2, 31.7] 23.2 [11.4, 34.9] 29.4 [19.8, 39.1]	<0.001 <0.001 <0.001	2.32 [1.59, 3.39] 2.83 [1.57, 5.13] 2.73 [1.88, 3.95]	<0.001 <0.001 <0.001
Week 56						
40mg eow (all) 40mg eow(300) 40mg ew	62/172 (36) 33/95 (35) 65/157 (41)	20/170 (12) 9/95 (10)	24.3 [15.6, 32.9] 25.3 [14.0, 36.5] 29.6 [20.5, 38.7]	<0.001 <0.001 <0.001	3.06 [1.94, 4.84] 3.67 [1.86, 7.24] 3.52 [2.24, 5.53]	<0.001 <0.001 <0.001
ITT population						
Week 26						
40mg eow (all) 40mg eow(300) 40mg ew	87/260 (34) 40/133 (30) 82/257 (32)	36/261 (14) 15/147 (10)	19.7 [12.6, 26.8] 19.9 [10.7, 29.1] 18.1 [11.0, 25.2]	<0.001 <0.001 <0.001	2.43 [1.71, 3.43] 2.95 [1.71, 5.08] 2.31 [1.63, 3.29]	<0.001 <0.001 <0.001
Week 56						

40mg eow (all) 40mg eow(300) 40mg ew	76/260 (29.2) 36/133 (27) 78/257 (30)	27/261 (10) 12/147 (8)	18.9 [12.2, 25.5] 18.9 [10.2, 27.7] 20.0 [13.3, 26.7]	<0.001 <0.001 <0.001	2.83 [1.89, 4.23] 3.32 [1.80, 6.10] 2.93 [1.96, 4.39]	<0.001 <0.001 <0.001
CLASSIC-II double-blind treatment groups						
Week 24						
40mg eow 40mg ew	11/19 (58) 17/18 (94)	7/18 (39)	19.0 [-12.6, 50.6] 55.6 [30.7, 80.4]	0.33 0.001	1.49 [0.74, 2.98] 2.43 [1.35, 4.38]	0.26NS 0.003
Week 56						
40mg eow 40mg ew	9/19 (47) 12/18 (67)	6/18 (33)	14.0 [-17.2, 45.3] 33.3 [2.5, 64.1]	0.38 0.034	1.42 [0.63, 3.19] 2.00 [0.96, 4.15]	0.39NS 0.063

[a:] mITT=CR-70 responders at week 4 following open-label adalimumab induction

Proportion of subjects on infliximab in clinical remission at week 30 and week 54 who had a clinical response (CR-70 and ≥ 25% in CDAI) at week 2 of ACCENT I

	Infliximab n/N (%)	Placebo n/N (%)	Risk difference [95%CI]	p- value	Relative Risk [95%CI]	p- value
Week 30						
5mg/kg 10mg/kg	44/113 (39) 50/112 (45)	23/110 (21)	18.0 [5.3, 29.8] 23.7 [11.8, 35.7]	0.0027 0.0001	**1.86 [1.21, 2.86]** 2.14 [1.41, 3.24]	**0.0047** 0.0004
Week 54						
5mg/kg 10mg/kg	32/113 (28) 43/112 (38)	15/110 (14)	14.7 [4.2, 25.2] 24.8 [13.7, 35.8]	0.006 <0.0001	2.08 [1.19, 3.62] 2.82 [1.67, 4.76]	0.01 0.0001

9. Clinical Claim

The submission claimed that treatment with adalimumab leads to significantly better efficacy and equivalent safety compared to placebo. Furthermore, the submission claimed that adalimumab is associated with greater efficacy than infliximab 5 mg/kg and has at least equal efficacy to infliximab 10 mg/kg.

The PBAC considered efficacy of adalimumab compared to placebo had been established in varying induction and maintenance dosage regimens that were reasonably consistent (though not identical) with the proposed listing.

The PBAC further considered the claim that adalimumab is superior to infliximab was not adequately demonstrated on the evidence provided, but agreed that adalimumab is probably equivalent to infliximab 5mg/kg and may have an advantage for patients because of the subcutaneous route of administration.

10. Economic Analysis

The equi-effective doses in terms of cost-minimisation were claimed by the submission to be adalimumab 160 mg at week 0 and 80mg week 2, then 40mg every other week thereafter and infliximab 5mg/kg (weeks 0, 2 6 and every 8 weeks thereafter). These were accepted by the PBAC.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of patients receiving adalimumab will be less than 10,000 per year in the first five years of listing at a cost of approximately less than $10 million in year 1 and between $30 and $60 million in year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of adalimumab on the PBS for the treatment of patients with moderate to severe Crohn disease (Crohn Disease Severity Index (CDAI) ≥ 300) or in patients with an ileostomy or colectomy due to Crohn disease on a cost-minimisation basis compared with infliximab. The PBAC considered the equi-effective doses to be adalimumab 160 mg at week 0 and 80mg week 2, then 40mg every other week thereafter and infliximab 5mg/kg (weeks 0, 2, 6 and every 8 weeks thereafter).

The PBAC agreed that the Crohn disease listing for adalimumab should be identical to infliximab, although there should be no specific listing for the paediatric population as adalimumab has not been trialled in children, and that the interchangeability rules should be the same as the rules which apply to the bDMARDs for other PBS-listed conditions.

The PBAC considered that patients should continue on adalimumab only if they were in remission (i.e. CDAI ≤ 150) and not as proposed in the alternative listing in the submission of a decrease of ≥ 150 points, as the ICER for this continuation rule was unacceptably high.

Despite recommending that interchangeability rules should apply, the PBAC recognised there was a lack of evidence about the appropriateness of such rules for Crohn disease. The Committee decided it wished to investigate interchangeability rules in general and requested data from Medicare Australia concerning the interchangeability of the bDMARDs in other conditions, with emphasis on how effective the agents were when prescribed after failure of the first bDMARD.

With regards to the grandfathering request, the PBAC recommended that the same requirements be applied to patients seeking grandfathering onto PBS subsidised treatment with adalimumab for Crohn Disease as are currently applied to the infliximab PBS listing for this indication. This would allow initial supply of PBS-subsidised adalimumab to a patient with a CDAI Score of greater than or equal to 300 prior to commencing treatment with adalimumab, who has demonstrated or sustained an adequate response to treatment with adalimumab, defined as a reduction in CDAI Score to no greater than 150.

A separate grandfather clause for patients with short gut syndrome or "-ostomy" patients, allows initial supply of PBS-subsidised adalimumab if the patient has a history of extensive small intestinal disease with radiological evidence of intestinal inflammation affecting more than 50cm of the small intestine, has diagnostic imaging or surgical evidence of short gut syndrome, or has an ileostomy or colostomy with a documented history of intestinal inflammation, and has demonstrated or sustained an adequate response to treatment with adalimumab according to the criteria included in the relevant continuation restriction.

The PBAC did not consider it appropriate to grandfather all patients entered in the sponsor's clinical trial M02-04 regardless of their CDAI score at baseline or their subsequent response, as this would create inequities between these and other patients. The PBAC expressed its hope that when agreeing to enrol in this clinical trial, all patients were properly informed about the consequences of the product not being recommended for PBS subsidy for their condition.

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

Abbott Australasia welcomes the PBAC's decision to recommend Humira for listing on the PBS for use in the treatment of Crohn disease.