PUBLIC SUMMARY DOCUMENT
Product: Adalimumab, injection, 40 mg in 0.8 mL, pre-filled syringe, pre-filled pen, Humira®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission requested an extension to the current Authority Required PBS listing for Crohn disease to include patients with fistulae.

2. Background

Adalimumab had not previously been considered by the PBAC for the fistulising Crohn disease indication.

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

At the March 2010 PBAC meeting, infliximab was recommended for listing as a pharmaceutical benefit under Section 100 (Highly Specialised Drugs Program) for treatment of complex refractory fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula, on the basis of a high, but acceptable, cost-effectiveness ratio, in the context of a serious medical condition that has a large impact on the quality of life of often otherwise healthy younger patients.

In terms of assessment for continuing therapy, the PBAC accepted that response could be assessed as either closure of at least 50% of the number of externally draining fistulae (i.e. no drainage despite finger pressure in at least 50% of fistulae) or a marked reduction in drainage of all fistulae together with less pain and induration as reported by the patient.

3. Registration Status

Adalimumab was TGA registered on 26 June 2007 for 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 had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab.

The PBAC considered fistulising disease to be a manifestation of moderate to severe Crohn disease, and that it was reasonable to interpret that the TGA approved indication includes patients with fistulising disease.

4. Listing Requested and PBAC's View

The submission requested a restriction similar to that for infliximab for fistulising Crohn disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Adalimumab is proposed as an alternative treatment to infliximab for fistulising Crohn disease.

6. Comparator

The submission nominated infliximab as the comparator. The PBAC agreed that this was appropriate.

7. Clinical Trials

The submission presented an indirect comparison of adalimumab and infliximab with placebo as the common reference using a sub-group of adalimumab treated patients who had fistulae from the CHARM study (the CHARM sub-group) and infliximab treated patients from ACCENT II.

In the CHARM study, patients with moderate to severe Crohn disease (CDAI ≥ 220 - ≤ 450) were treated with 80 mg adalimumab at week 0, and 40 mg adalimumab at week 2 and subsequently randomised to adalimumab 40 mg every other week or placebo. In ACCENT II, patients with fistulising Crohn disease were treated with infliximab 5 mg/kg at weeks 0, 2 and 6 and were subsequently randomised to infliximab (5 mg/kg every 8 weeks) or placebo maintenance. Publication details of the studies presented in the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Adalimumab (common reference placebo)		
CHARM Colombel J-F, et al.	Adalimumab for the treatment of fistulas in patients with Crohn disease.	*Gut* 2009; 58: 940-948
Colombel J-F, et al.	Adalimumab for maintenance of clinical response and remission in patients with Crohn disease: The CHARM trial.	*Gastroenterology* 2007; 132: 52-65
Feagan BG, et al.	Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn disease: results from the CHARM study.	*Gastroenterology* 2008; 135 1493-1499
Infliximab (common reference placebo)		
ACCENT II Sands BE, et al.	Infliximab maintenance therapy for fistulising Crohn disease.	*New England Journal of Medicine* 2004; 350(9): 876-885
Sands BE, et al.	Maintenance infliximab does not result in increased abscess development in fistulising Crohn disease: results from the ACCENT II study.	*Alimentary Pharmacol & Therapeutics* 2006; 23: 1127-1136
Sands BE, et al.	Long-term treatment of rectovaginal fistulas in Crohn disease: response to infliximab in the ACCENT II study.	*Clinical Gastroenterology and Hepatology* 2004; 2: 912-920
Lichtenstein GR, et al.	Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulising Crohn disease.	*Gastroenterology* 2005; 128: 862-869
Lichtenstein GR, et al.	Clinical trial: Benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomised trials.	*Alimentary Pharmacol & Therapeutics* 2009; 30: 210-226

The PBAC noted that there were different inclusion and exclusion criteria between the CHARM and ACCENT II trials which suggested that patients treated with adalimumab had more severe disease. For the CHARM trial, selection was primarily based on a CDAI score of ≥ 220, ≤ 450 and the presence of fistulae was not an entry criterion. Selection in ACCENT II was based on the presence of chronic fistulae irrespective of the CDAI. Under the PBS eligibility criteria for the severe refractory Crohn indication (CDAI ≥ 300), 60% of patients in the CHARM trial and 34% of patients in ACCENT II would be PBS eligible. The PBAC noted the sponsor's pre-PBAC response which claimed that baseline CDAI score is not a significant treatment effect modifier. The PBAC also noted the lower induction dose of adalimumab used in the CHARM trial (80 mg at week 0, 40 mg at week 2) compared with the TGA-approved doses for adalimumab in Crohn disease (i.e. 160 mg at week 0 and 80 mg at week 2), and the small number of patients in the CHARM sub-group (n=30).

8. Results of Trials

The results for the CHARM sub-group were those for whom response and non-response was demonstrated at week 4 (following the induction doses) and those for the ACCENT II trial were only those for patients who achieved a response at both weeks 10 and 14 of the trial and thus assessed the maintenance of that response. The submission argued that as the CHARM sub-group included both responders and non-responders, this would bias against adalimumab, however the PBAC considered that it was possible that this may favour adalimumab as the response rates reported at 26 and 56 weeks may include those patients who had an initial response and maintained it as well as patients who achieved response after prolonged exposure to adalimumab.

The table below summarises the comparative effectiveness of adalimumab and infliximab in terms of complete fistula closure at week 56.

Proportion of subjects with complete fistula closure at trial endpoint (week 56)

	Adalimumab n/N (%)	Placebo n/N (%)	Infliximab n/N (%)	RD (95%CI) p-value	RR (95%CI) p-value
CHARM sub-group	11/30 (36.7%)	6/47 (12.8%)	-	**23.9 (4.2, 43.6) p=0.018**	**2.87 (1.19, 6.95) p=0.019**
ACCENT II	-	19/98 (19.4%)	33/91 (36.3%)	**16.9 (4.3, 29.5) p=0.009**	**1.87 (1.15, 3.04) p=0.012**
Indirect comparison: Indirect RR (95%CI)				1.54 (0.54, 4.21)	
Indirect comparison: Indirect OR (95%CI)				1.67 (0.45,6.20)	

Abbreviations: RD: risk difference; RR: relative risk; CI: confidence interval; OR: odds ratio.
Bold typography indicates statistically significant differences

The efficacy analyses of complete fistula closure data in the CHARM sub-group were performed on the intention-to-treat (ITT) sub-group dataset to analyse drug effect on fistulae in all subjects with draining cutaneous fistulae, whilst efficacy analyses of fistula data in ACCENT II were performed on the modified ITT dataset and did not include non-responders. The submission stated that the ACCENT II analysis may overestimate the efficacy of infliximab as it does not include initial non-responders, however this is more representative of the PBS restriction where only responders at week 12 are eligible to continue treatment. As a result, an indirect comparison of outcomes from the two trials may be biased in favour of infliximab. However, as the CHARM sub-group included responders and non-responders, the PBAC considered that the reported number of responders at week 56 may be

overestimated as these patients may include some patients who achieved treatment response over time with prolonged exposure to adalimumab (i.e. >12 weeks), which is not consistent with the proposed restriction, rather than only those who achieved response after initial treatment and maintained that response.

The PBAC noted that the placebo arms of the CHARM sub-group and ACCENT II were not comparable. In the CHARM sub-group, all patients received the induction doses (80 mg at week 0 and 40 mg at week 2) and were subsequently randomised to adalimumab or placebo. This is in contrast to the proposed initial treatment with adalimumab (160 mg at week 0, 80 mg at week 2 and 40 mg every other week thereafter for a maximum of 16 weeks) and assessment of response at week 12. Conversely, all patients in ACCENT II received the induction doses of infliximab (at weeks 0, 2 and 6, consistent with its PBS restriction) and were subsequently randomised to infliximab or placebo maintenance. The PBAC considered that given the placebo arm of the CHARM sub-group did not receive the full initial treatment, unlike those in ACCENT II, it is possible that the response rate in the placebo arm of the CHARM sub-group is underestimated.

The submission presented an analysis to estimate maintenance of response which compared only patients with an initial response, and demonstrated the efficacy of the treatments in maintaining that response.

The results of the indirect comparison suggested that there was no difference in the proportion of responders with a loss of response at study endpoint between patients treated with adalimumab and infliximab. However, it was noted that this analysis was informed by only a small number of patients and therefore the results were only indicative.

No new safety concerns for either adalimumab or infliximab were identified from those already known to be associated with each of the treatments.

9. Clinical Claim

The submission described adalimumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over infliximab.

The PBAC recalled that adalimumab and infliximab have been shown to be equivalent in other indications and considered that the submission's claim of non-inferiority in fistulising Crohn disease was not unreasonable.

10. Economic Analysis

The submission claimed cost-minimisation for adalimumab with infliximab, although no cost-minimisation analysis was presented. The price requested for adalimumab for fistulising Crohn disease was the same as that for its current listing for severe refractory Crohn disease. This was accepted by the PBAC. The equi-effective doses have previously been accepted by the PBAC as adalimumab 160 mg at week 0, 80 mg at week 2 and 40 mg every second week for maintenance subject to response and infliximab 5 mg/kg at week 0, 2 and 6 and every eight weeks thereafter subject to response for severe refractory Crohn disease.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 10,000 in Year 5 for the total population eligible for both adalimumab and infliximab.

The financial cost per year to the PBS was estimated in the submission to be in the range of $10 – 15 million in Year 1 for the total market size of adalimumab and infliximab.

These were considered possible underestimates.

12. Recommendation and Reasons

The PBAC recommended the listing of adalimumab on the PBS as an Authority Required benefit for the treatment of complex, refractory fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula on a cost-minimisation basis with infliximab, at the same price as the current listing for adalimumab for severe refractory Crohn disease.

The PBAC noted the TGA approved indication for adalimumab is for treatment of moderate to severe Crohn disease, without specific reference to fistulising disease. However, the PBAC considered fistulising disease to be a manifestation of moderate to severe Crohn disease, and that it was reasonable to interpret that the TGA approved indication includes patients with fistulising disease.

The PBAC considered a restriction consistent with the current listing for infliximab for fistulising disease, using the same adalimumab doses used in the listing for severe refractory Crohn disease was appropriate. The PBAC recommended that patients be permitted to cycle between PBS-subsidised infliximab and adalimumab using similar criteria to those for the severe refractory Crohn disease listings.

The PBAC noted that a proportion of patients with fistulising disease and a CDAI score $\geq$ 300 are already able to access PBS-subsidised adalimumab under the current Crohn disease listing. However, there may be patients with worse fistulae but with a lower CDAI who are not currently eligible and that this represents an equity issue. The PBAC noted that the presence of fistulae adds only around 20 points to the overall CDAI score. The PBAC also noted that there was a high clinical need for an alternative treatment that can be given by an alternative route other than intravenously and that morbidity of the disease is high.

The PBAC agreed that infliximab was the appropriate comparator.

The PBAC considered there were a number of areas of uncertainty with the indirect comparison presented in the submission, which used a sub-group of adalimumab treated patients with fistulae from the CHARM trial, and infliximab treated patients from ACCENT-II, with placebo as the common reference. Specifically, the PBAC noted the lower induction dose of adalimumab used in the CHARM trial (80 mg at week 0, 40 mg at week 2) compared with the TGA approved doses for Crohn disease (160 mg at week 0, 80 mg at week 2). There were also differences in the inclusion and exclusion criteria between the trials which suggest that patients treated with adalimumab had more severe disease. The PBAC noted the sponsor's pre-PBAC response which claimed that baseline CDAI score is not a significant treatment effect modifier. The PBAC also noted the small number of patients in the CHARM sub-group (n=30).

The PBAC noted that the results of the indirect comparison suggested that patients treated with adalimumab are more likely to have complete fistula closure compared with patients treated with infliximab (RR=1.54, [95% CI 0.54, 4.21]). The difference was not statistically significant, however, the trials were not specifically powered to detect differences in this outcome. The PBAC considered that, as adalimumab and infliximab have been shown to be equivalent in other indications and have been cost-minimised in Crohn disease, a cost-minimisation recommendation was acceptable on the basis of the data presented and high clinical need.

The PBAC noted the consumer comments for this item.

Recommendation:
ADALIMUMAB, injection, 40 mg in 0.8 mL, pre-filled syringe, pre-filled pen

Extend the current restriction to include:

NOTE:
Any queries concerning the arrangements to prescribe adalimumab may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application Forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au.

Written applications for authority to prescribe adalimumab should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

NOTE:
TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of adalimumab and infliximab for patients with complex refractory fistulising Crohn disease. Where the term 'tumour necrosis factor (TNF) alfa antagonist' appears in the following NOTES and restrictions, it refers to adalimumab and infliximab only.

A patient is eligible for PBS-subsidised treatment with only 1 of the 2 TNF-alfa antagonists at any 1 time.

From [start date], under the PBS, all patients will be able to commence a treatment cycle where they may trial each PBS-subsidised TNF-alfa antagonist without having to experience a disease flare when swapping to the alternate agent. Under these interchangeability arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a TNF-alfa antagonist while they continue to show a response to therapy.

A patient who received PBS-subsidised TNF-alfa antagonist treatment prior to [start date] is considered to be in their first cycle as of [start date].

Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised TNF-alfa antagonist more than twice.

Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised TNF-alfa antagonist therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the

last approval for PBS-subsidised TNF-alfa antagonist treatment in the most recent cycle to the date of the first application for initial treatment with a TNF-alfa antagonist under the new treatment cycle.

A patient who has failed fewer than 3 trials of TNF-alfa antagonists in a treatment cycle and who has a break in therapy of less than 5 years, may commence a further course of treatment within the same treatment cycle.

A patient who has failed fewer than 3 trials of TNF-alfa antagonists in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle.

There is no limit to the number of treatment cycles a patient may undertake in their lifetime.

(1) How to prescribe PBS-subsidised TNF-alfa antagonist therapy after [start date].

(a) Initial treatment.
Applications for initial treatment should be made where:
(i) a patient has received no prior PBS-subsidised TNF-alfa antagonist treatment in this treatment cycle and wishes to commence such therapy (Initial 1); or
(ii) a patient has received prior PBS-subsidised (initial or continuing) TNF-alfa antagonist therapy and wishes to trial an alternate agent (Initial 2) [further details are under 'Swapping therapy' below]; or
(iii) a patient wishes to re-commence treatment with a specific TNF-alfa antagonist following a break in PBS-subsidised therapy with that agent (Initial 2).

Initial treatment authorisations will be limited to provide for a maximum of 16 weeks of therapy for adalimumab and 14 weeks of therapy for infliximab.

From [start date], a patient must be assessed for response to any course of initial PBS-subsidised treatment following a minimum of 12 weeks of therapy for adalimumab and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab, and this assessment must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased.

Where a response assessment is not submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with that TNF-alfa antagonist.

For second and subsequent courses of PBS-subsidised TNF-alfa antagonist treatment, it is recommended that a patient is reviewed in the month prior to completing their current course of treatment and that an application is posted to Medicare Australia no later than 2 weeks prior to the patient completing their current treatment course.

Adalimumab only: Two completed authority prescriptions must be submitted with every initial application for adalimumab. One prescription must be for the induction pack containing a quantity of 6 doses of 40 mg and no repeats. The second prescription must be written for 2 doses of 40 mg and 2 repeats.

(b) Continuing treatment. Following the completion of an initial treatment course with a specific TNF-alfa antagonist, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing TNF-alfa antagonist treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

It is recommended that a patient be reviewed in the month prior to completing their current course of treatment to ensure uninterrupted TNF-alfa antagonist supply.

Assessments of response to a course of PBS-subsidised therapy must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased.

Where a response assessment is not submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with that TNF-alfa antagonist.

(2) Swapping therapy.

Once initial treatment with the first PBS-subsidised TNF-alfa antagonist is approved, a patient may swap if eligible to the alternate TNF-alfa antagonist within the same treatment cycle.

A patient may trial the alternate TNF-alfa antagonist at any time, regardless of whether they are receiving therapy (initial or continuing) with a TNF-alfa antagonist at the time of the application. However, they cannot swap to a particular TNF-alfa antagonist if they have failed to respond to prior treatment with that drug two times within the same treatment cycle.

To ensure a patient receives the maximum treatment opportunities allowed under the interchangeability arrangements, it is important that they are assessed for response to every course of treatment approved, within the timeframes specified in the relevant restriction.

To avoid confusion, an application for a patient who wishes to swap to the alternate TNF-alfa antagonist should be accompanied by the approved authority prescription or remaining repeats for the TNF-alfa antagonist the patient is ceasing.

(3) Baseline measurements to determine response.

Medicare Australia will determine whether a response to treatment has been demonstrated based on the baseline measurements submitted with the first authority application for a TNF-alfa antagonist. However, prescribers may provide new baseline measurements any time that an initial treatment authority application is submitted within a treatment cycle and Medicare Australia will assess response according to these revised baseline measurements.

(4) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy.

A patient who wishes to trial a second or subsequent treatment cycle following a break in PBS-subsidised TNF-alfa antagonist therapy of at least 5 years, must requalify for initial treatment with respect to the indices of disease severity.

(5) Patients 'grandfathered' onto PBS-subsidised treatment with adalimumab or infliximab.

A patient who commenced treatment with adalimumab for complex refractory fistulising Crohn disease prior to 4 November 2010 or infliximab prior to 1 March 2010 and who continues to receive treatment at the time of application, may qualify for treatment under the initial 'grandfather' treatment restriction.

A patient may only qualify for PBS-subsidised treatment under this criterion once. A maximum of 24 weeks of treatment with adalimumab or infliximab will be authorised under this criterion.

Following completion of the initial PBS-subsidised course, further applications for treatment with adalimumab or infliximab will be assessed under the continuing treatment restriction.

'Grandfather' arrangements will only apply for the first treatment cycle. For the second and subsequent cycles, a 'grandfather' patient must requalify for initial treatment under the criteria that apply to a new patient. See 'Re-commencement of treatment after a 5-year break in PBS-subsidised therapy' above for further details.

No applications for increased maximum quantities and/or repeats will be authorised.

Authority Required

Initial 1

Initial treatment of complex refractory FISTULISING CROHN DISEASE.

Initial PBS-subsidised treatment with adalimumab by a gastroenterologist or a consultant physician as specified in the NOTE below, of a patient with complex refractory fistulising Crohn disease who:
(a) has confirmed Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician as specified in the NOTE below; and
(b) has an externally draining enterocutaneous or rectovaginal fistula; and

(c) has signed a patient acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment.

NOTE: Prescribers must be gastroenterologists (code 87), consultant physicians [internal medicine specialising in gastroenterology (code 81)] or consultant physicians [general medicine specialising in gastroenterology (code 82)].

Authority applications must be made in writing and must include:
(a) two completed authority prescription forms; and
(b) a completed Fistulising Crohn Disease PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:
(i) a completed current Fistula Assessment Form including the date of assessment of the patient's condition; and
(ii) a signed patient acknowledgement.

The most recent fistula assessment must be no more than 1 month old at the time of application.

A maximum of 16 weeks treatment will be authorised under this criterion.

Two completed authority prescriptions must be submitted with every initial application for adalimumab. One prescription must be for the induction pack containing a quantity of 6 doses of 40 mg and no repeats. The second prescription must be written for 2 doses of 40 mg and 2 repeats. Where fewer than 2 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete a maximum of 16 weeks of treatment with adalimumab may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period.

An assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated.

This assessment must be submitted to Medicare Australia no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with adalimumab.

It is recommended that an application for continuing treatment is posted to Medicare Australia at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised adalimumab treatment.

Authority Required

Initial 2

Change or re-commencement of treatment of complex refractory FISTULISING CROHN DISEASE.

Initial PBS-subsidised treatment with adalimumab of complex refractory fistulising Crohn disease by a gastroenterologist or a consultant physician as specified in the NOTE below, of a patient with complex refractory fistulising Crohn disease who:
(a) has a documented history of complex refractory fistulising Crohn disease; and
(b) in this treatment cycle, has received prior PBS-subsidised treatment with adalimumab or infliximab for a draining enterocutaneous or rectovaginal fistula; and
(c) has not failed PBS-subsidised therapy with adalimumab for this condition more than once in the current treatment cycle.

NOTE: Prescribers must be gastroenterologists (code 87), consultant physicians [internal medicine specialising in gastroenterology (code 81)] or consultant physicians [general medicine specialising in gastroenterology (code 82)].

To demonstrate a response to treatment the application must be accompanied by the results of the most recent course of TNF-alfa antagonist therapy within the time frames specified in the relevant restriction.

Where the most recent course of PBS-subsidised TNF-alfa antagonist treatment was approved under an initial treatment restriction, the patient must have been assessed for response to that course following a minimum of 12 weeks of therapy for adalimumab and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab and this assessment must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased.

If the response assessment to the previous course of TNF-alfa antagonist treatment is not submitted as detailed above, the patient will be deemed to have failed therapy with that particular course of TNF-alfa antagonist.

Authority applications must be made in writing and must include:
(a) two completed authority prescription forms; and
(b) a completed Fistulising Crohn Disease PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:

(i) a completed current Fistula Assessment Form including the date of assessment of the patient's condition; and
(ii) details of prior TNF-alfa antagonist treatment including details of date and duration of treatment.

The most recent fistula assessment must be no more than 1 month old at the time of application.

A maximum of 16 weeks treatment will be authorised under this criterion.

Two completed authority prescriptions must be submitted with every initial application for adalimumab. One prescription must be for the induction pack containing a quantity of 6 doses of 40 mg and no repeats. The second prescription must be written for 2 doses of 40 mg and 2 repeats. Where fewer than 2 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete a maximum of 16 weeks of treatment with adalimumab may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period.

An assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated.

This assessment must be submitted to Medicare Australia no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with adalimumab.

It is recommended that an application for continuing treatment is posted to Medicare Australia at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised adalimumab treatment.

Authority Required

Initial 3 (grandfather)

Initial PBS-subsidised treatment of complex refractory FISTULISING CROHN DISEASE in a patient who has previously received non-PBS-subsidised therapy with adalimumab.

Initial PBS-subsidised supply for continuing treatment with adalimumab by a gastroenterologist, a consultant physician as specified in the NOTE below, or other consultant physician in consultation with a gastroenterologist of a patient who satisfies the following criteria:
(a) has a documented history of complex refractory fistulising Crohn disease and was receiving treatment with adalimumab prior to 4 November 2010; and
(b) had a draining enterocutaneous or rectovaginal fistula(e) prior to commencing treatment with adalimumab; and

(c) has signed a patient acknowledgement indicating that they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment; and
(d) is receiving treatment with adalimumab at the time of application; and
(e) has demonstrated or sustained an adequate response to treatment with adalimumab.

NOTE: Prescribers must be gastroenterologists (code 87), consultant physicians [internal medicine specialising in gastroenterology (code 81)] or consultant physicians [general medicine specialising in gastroenterology (code 82)].

An adequate response to adalimumab treatment is defined as:
(a) a decrease from baseline in the number of open draining fistulae of greater than or equal to 50%; and/or
(b) a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient.

Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Fistulising Crohn Disease PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:
(i) a completed current and baseline Fistula Assessment form including the date of assessment of the patient's condition; and
(ii) a signed patient acknowledgement.

The current fistula assessment must be no more than 1 month old at the time of application.

The baseline fistula assessment must be from immediately prior to commencing treatment with adalimumab.

An assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to Medicare Australia no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criteria.

Where an assessment is not submitted to Medicare Australia within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with adalimumab.

A maximum of 24 weeks treatment will be approved under this criterion.

Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Patients may qualify for PBS-subsidised treatment under this restriction once only.

Authority Required

Continuing treatment of complex refractory FISTULISING CROHN DISEASE.

Continuing PBS-subsidised treatment with adalimumab by a gastroenterologist, a consultant physician as specified in the NOTE below or other consultant physician in consultation with a gastroenterologist, of a patient who:
(a) has a documented history of complex refractory fistulising Crohn disease; and
(b) has demonstrated or sustained an adequate response to treatment with adalimumab.

NOTE: Prescribers must be gastroenterologists (code 87), consultant physicians [internal medicine specialising in gastroenterology (code 81)] or consultant physicians [general medicine specialising in gastroenterology (code 82)].

An adequate response is defined as:

(a) a decrease from baseline in the number of open draining fistulae of greater than or equal to 50%; and/or
(b) a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient.

Authority applications must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Fistulising Crohn Disease PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes a completed Fistula Assessment form including the date of the assessment of the patient's condition.

The fistula assessment must be no more than 1 month old at the time of application.

If the application is the first application for continuing treatment with adalimumab, an assessment of the patient's response must be made following a minimum of 12 weeks after the first dose so that there is adequate time for a response to be demonstrated.

An assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to Medicare Australia no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criteria.

Where an assessment is not submitted to Medicare Australia within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with adalimumab.

Patients are eligible to receive continuing adalimumab treatment in courses of up to 24 weeks providing they continue to sustain the response.

A maximum of 24 weeks treatment will be authorised under this criterion.

Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Maximum quantity:	1 (x6)	Initial 1 and 2
	2 (x1)	All indications
Repeats:	0 (x6)	Initial 1 and 2
	2 (x1)	Initial 1 and 2
	5 (x1)	Initial 3 and Continuing

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

The Sponsor is pleased that patients will have a treatment alternative that can be administered subcutaneously for fistulising Crohn disease.