

7.07 ADALIMUMAB

40 mg/0.8 mL injection, 2 x 0.8 mL cartridges

40 mg/0.8 mL injection, 2 x 0.8 mL syringes

40 mg/0.8 mL injection, 6 x 0.8 mL cartridges

40 mg/0.8 mL injection, 6 x 0.8 mL syringes

Humira®, Abbvie Pty Ltd

1 Purpose of Application

1.1 The minor resubmission requested a Section 85, Authority Required listing for adalimumab for the treatment of patients with moderate to severe ulcerative colitis (UC).

2 Requested listing

2.1 The requested restriction was the same as with the July 2015 major resubmission which was similar to that for infliximab, with the exception of the age of the eligible population, which is restricted to 18 years and older, and the proposed listing under Section 85 (infliximab is listed under Section 100).

2.2 The minor resubmission requested the following changes to the proposed price for adalimumab:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ADALIMUMAB				
<u>Induction</u>				
40 mg in 0.8 mL injection, 6 x 0.8 mL cartridges	1	0	\$ [REDACTED]	Humira AbbVie
40 mg in 0.8 mL injection, 6 x 0.8 mL syringes	1	0	\$ [REDACTED]	
40 mg in 0.8 mL injection, 2 x 0.8 mL cartridges	1	2	\$*	
40 mg in 0.8 mL injection, 2 x 0.8 mL syringes	1	2	\$*	
<u>Maintenance</u>				
40 mg in 0.8 mL injection, 2 x 0.8 mL cartridges	1	5	\$*	
40 mg in 0.8 mL injection, 2 x 0.8 mL syringes	1	5	\$*	

*submission proposed the 2-pack would be priced equivalently to infliximab.

Section 85, Authority required (Streamlined)

Treatment phase:	Initial treatment (new patient)
Episodicity	For 12 weeks after the first dose
Condition	Moderate to severe UC
Treatment criteria	Must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)]. Applications for authorisation of initial treatment must be in writing and must include: (a) two completed authority prescription forms; AND (b) a completed UC PBS Authority Application - Supporting Information Form which includes the following:

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	<p>(i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; AND</p> <p>(ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy]; AND</p> <p>(iii) the signed patient acknowledgement.</p> <p>A maximum quantity and number of repeats to provide for an initial course of this drug consisting of 6 doses to be administered at weeks 0 (160mg), 2 (80mg), 4 (40mg), 6 (40mg), 8 (40mg) and 10 (40mg) will be authorised.</p> <p>All tests and assessments should be performed preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment. The most recent Mayo clinic or partial Mayo clinic score must be no more than 1 month old at the time of application.</p> <p>Patients who fail to achieve a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1, within the first 12 weeks of receiving this drug for UC, or have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1, with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.</p> <p>A partial Mayo clinic assessment of the patient's response to this initial course of treatment must be made up to 12 weeks after the first dose (2 weeks following the sixth dose) so that there is adequate time for a response to be demonstrated.</p> <p>The patient must have signed a patient acknowledgement indicating they understand and acknowledge that the PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment.</p> <p>If treatment with any of the above-mentioned drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree of this toxicity at the time of application.</p> <p>Patients may qualify for PBS-subsidised treatment under this restriction once only.</p>
Clinical criteria	<p>Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more months or have intolerance necessitating permanent treatment withdrawal, AND</p> <p>Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR</p> <p>Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR</p> <p>Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, AND</p> <p>Patient must have a Mayo clinic score greater than or equal to 6; OR</p> <p>Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).</p>
Population criteria	For patients 18 years old and older

Treatment phase: Maintenance treatment	
Episodicity	Maximum 5 repeats, 12 weeks after the initial course (maximum 24 weeks)
Condition	Moderate to severe UC
Treatment criteria	<p>Must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)].</p> <p>Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1, with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.</p>

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	<p>Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. Up to a maximum of 5 repeats will be authorised. No applications for increased repeats will be authorised.</p>
Clinical criteria	<p>Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug.</p>
Population criteria	For patients 18 years old and older

Treatment Phase: Initial PBS-subsidised treatment of moderate to severe ulcerative colitis in a patient who has previously received non-PBS-subsidised therapy with this drug (Grandfather).	
Episodicity	Maximum 5 repeats, 12 weeks after the initial course (maximum 24 weeks)
Condition	Moderate to severe UC
Treatment criteria	<p>Must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)].</p> <p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form; AND (b) a completed Ulcerative Colitis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed current and baseline Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; AND (ii) the date of commencement of this drug; AND (iii) the signed patient acknowledgement.</p> <p>The current Mayo clinic or partial Mayo clinic assessment must be no more than 1 month old at the time of application. The baseline assessment must be from immediately prior to commencing treatment with this drug.</p> <p>Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. Up to a maximum of 5 repeats will be authorised. No applications for increased repeats will be authorised.</p> <p>The patient must have signed a patient acknowledgement indicating they understand and acknowledge that the PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment.</p> <p>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
Clinical criteria	<p>Patient must have been receiving treatment with this drug prior to [DATE OF PBS LISTING], AND Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing treatment with this drug; OR Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score) prior to commencing treatment with this drug; OR Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced treatment with this drug where a Mayo clinic or partial Mayo clinic baseline assessment is not available, AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug.</p>

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Population criteria	Patient must be 18 years of age or older.
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Treatment Phase: Balance of supply	
Episodicity	Maximum 5 repeats, 12 weeks after the initial course (maximum 24 weeks)
Condition	Moderate to severe UC
Treatment criteria	Must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria	Patient must have received insufficient therapy with this drug under the Initial treatment (new patient) restriction to complete the 6 doses (i.e. the initial infusion regimen at weeks 0, 2, 4, 6, 8 and 10 weeks); OR Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks of treatment; OR Patient must have received insufficient therapy with this drug to complete 24 weeks of treatment under the Initial PBS-subsidised treatment restriction for patients who had previously received non-PBS subsidised treatment (Grandfathered patient), AND The treatment must provide no more than the balance of up to 6 doses (new patients) or 5 repeats (Continuing patients or Grandfathered patients).
Population criteria	Patient must be 18 years of age or older

Source: July 2015 resubmission

For more details on PBAC's view, see section 7 "PBAC outcome".

3 Background

- 3.1 Adalimumab was TGA registered on 23 July 2013 for the treatment of moderate to severe UC.
- 3.2 This was the fourth submission for adalimumab in UC. The first submission was November 2013, the second submission was July 2014 and the third submission was July 2015.

Table 1: Summary of the previous resubmission and current resubmission for adalimumab in UC

	July 2015: Previous major resubmission	November 2015: Current minor resubmission
Requested PBS listing	The restriction was updated to be aligned with infliximab's restriction for moderate to severe UC with the exception that the adalimumab restriction does not include paediatric patients. PBAC comment: The PBAC considered that the exclusion of paediatric patients from the restriction was not adequately justified and should be addressed in any future major resubmission. [7-2 adalimumab PBAC minutes July 2015, Item 7.01].	Unchanged
Requested price	The DPMQ for: 6 x 40 mg ADA = \$ [REDACTED] 2 x 40 mg ADA = \$ [REDACTED] Specific terms for an RSA were not proposed, however the sponsor was willing to enter into a RSA.	The DPMQ for: 6 x 40 mg ADA = \$ [REDACTED] 2 x 40 mg ADA = same price as infliximab. Sponsor notes there is a Special Pricing Arrangement for infliximab and the price offer [REDACTED] % [REDACTED] from the July 2015 resubmission
Main comparator	Infliximab	Infliximab
Clinical evidence	An indirect comparison between adalimumab and infliximab was presented. It included the previously presented ULTRA 1 and ULTRA 2 trials plus Suzuki (2014) (n=274) and three Infliximab trials: included: ACT 1 (n=n364), ACT 2 (n=364), Probert (2003) (n=n43) In addition, an indirect comparison to vedolizumab using GEMINI I (n=747, 374 induction and 373 maintenance) was included in an Attachment.	No new clinical evidence presented.
Clinical claim	The breadth of evidence suggests no statistically significant differences in efficacy and considered similar in safety for adalimumab vs infliximab (p152, of the resubmission). PBAC Comment: PBAC considered that the indirect comparisons presented in the resubmission provided low certainty evidence for the claim on non-inferiority between adalimumab and infliximab, both in the remission phase and in the maintenance phase. [7-7 adalimumab PBAC minutes July 2015, Item 7.01].	[REDACTED]

	July 2015: Previous major resubmission	November 2015: Current minor resubmission
Economic evaluation	Cost-minimisation analysis versus infliximab. PBAC Comment: PBAC did not consider that the resubmission had conclusively demonstrated that adalimumab was non-inferior to infliximab, it also did not accept the cost-minimisation analysis. [7-9 adalimumab PBAC minutes July 2015, Item 7.01].	No economic evaluation presented.
Number of patients	█ in Year 1 increasing to █ in Year 5.	Unchanged
Estimated total cost to PBS	\$█ in Year 1 increasing to \$█ in Year 5 for a total of \$█ over the first 5 years of listing.	The resubmission updated the financial estimates to reflect the █% price reduction offer for the █. \$█ in Year 1 increasing to \$█ in Year 5 for a total of \$█ over the first 5 years of listing.
PBAC decision	The PBAC rejected the request to extend the PBS listing for adalimumab to include the treatment of moderate to severe UC on the basis that the evidence presented did not establish non-inferiority of adalimumab to the nominated comparator (infliximab).	-

Source: Compiled during evaluation

For more details on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

- 4.1 Treatment of moderate to severe UC after failure of conventional agents (5-aminosalicylic acid compounds, corticosteroids, and immunomodulators), reflecting that of infliximab (i.e. first-line biologic therapy). At its July 2015 meeting, the PBAC considered that non-inferiority between adalimumab and infliximab was not demonstrated, however, the PBAC considered the clinical positioning to be unreasonable and that adalimumab may be more appropriately placed as a subsequent-line biologic, following failure of, or intolerance to, infliximab or vedolizumab [7-3 adalimumab PBAC minutes July 2015, Item 7.01].
- 4.2 The resubmission disagreed with the PBAC and maintained that it would not address the inequity in access. The resubmission focused on access issues in rural and remote Australia as well as the distribution of adalimumab in these areas.

For more details on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 The previous major resubmission considered by the PBAC in July 2015 nominated infliximab as comparator. This was accepted by the PBAC.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adalimumab including the ability of patients to treat themselves at home and improvements in terms of quality of life associated with not being required to travel long distances (particularly in the case of patients in remote areas) and spend time being treated at hospital.

6.3 The PBAC noted the correspondence received from Australian Inflammatory Bowel Disease Association, Gastroenterological Society of Australia and Crohn's and Colitis Australia clarifying the likely use of adalimumab in clinical practice.

Clinical trials

6.4 As a minor resubmission, no new clinical trials were presented.

Clinical claim

6.5 The minor resubmission maintained that adalimumab was non-inferior to infliximab and that this was supported by real world evidence presented in the July 2015 resubmission. However, the resubmission acknowledged the PBAC's conclusion in the July 2015 consideration where adalimumab was inferior to infliximab in the induction phase.

6.6 The PBAC did not accept the resubmission's claim of non-inferiority against infliximab.

Economic analysis

6.7 As a minor resubmission, there was no economic comparison presented.

Estimated PBS usage & financial implications

6.8 The minor resubmission updated the financial estimates [REDACTED]. The resubmission used the number of patients and number of induction packs from the July 2015 major resubmission.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Major resubmission July 2015					
Estimated extent of use					
Number treated	■	■	■	■	■
6 x 40 mg induction packs dispensed	■	■	■	■	■
2 x 40 mg continuation packs dispensed	■	■	■	■	■
Estimated total cost to PBS/RPBS (excluding co-payments)					
Total cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Estimated total net cost to PBS/RPBS (excluding co-payments)					
Net cost PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Minor resubmission November 2015					
Number treated	■	■	■	■	■
6 x 40 mg induction packs dispensed	■	■	■	■	■
2 x 40 mg induction packs dispensed	■	■	■	■	■
Estimated total cost to PBS/RPBS (excluding co-payments)					
Total cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Estimated total net cost to PBS/RPBS (excluding co-payments)					
Net cost to PBS/RPBS	-\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 5 of the minor resubmission p14 and Section E attachment of the minor resubmission

- 6.9 The net financial implications were estimated to be -\$■ (saving) in Year 1 increasing to \$■ in Year 5 for a total of \$■ less than \$10 million over the first 5 years of listing. These implications only assumed a reduced use of infliximab and did not factor the market share of adalimumab with the recent listing of vedolizumab.

For more details on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC rejected the request to extend the PBS listing of adalimumab for the treatment of patients with moderate to severe ulcerative colitis on the basis that the evidence presented in the July 2015 PBAC meeting did not support the non-inferiority claim in the maintenance phase against infliximab.
- 7.2 The PBAC noted that the proposed restriction was unchanged in the resubmission. The PBAC maintained its previous consideration from the July 2015 meeting that the exclusion of paediatric patients from the adalimumab restriction was not adequately justified and should be addressed in any future resubmission.
- 7.3 The PBAC reaffirmed its views from the July 2015 meeting that the clinical positioning of adalimumab may be more appropriately placed as a subsequent-line biologic, following failure of, or intolerance to, infliximab or vedolizumab (adalimumab PSD, July 2015).
- 7.4 The PBAC recalled that it had previously accepted infliximab as the appropriate comparator.

- 7.5 The PBAC noted that no new data were presented in the resubmission. The PBAC recalled the July 2015 PBAC meeting where it considered an indirect comparison based on three randomised controlled trials (RCTs) comparing adalimumab to placebo (ULTRA 1, ULTRA 2 and Suzuki 2014) and three RCTs comparing infliximab to placebo (ACT 1, ACT 2 and Probert). The indirect comparison provided low certainty evidence for the claim on non-inferiority between adalimumab and infliximab, both in the remission phase and in the maintenance phase (adalimumab PSD, July 2015).
- 7.6 The PBAC noted that the current resubmission [REDACTED]. The PBAC did not accept the non-inferiority claim in the maintenance phase. The PBAC reiterated its previous conclusions from the July 2015 PBAC meeting that the risk of bias was high for the maintenance phase. The data for the maintenance phase were incomplete due to a large number of discontinuations and substantial loss to follow-up (adalimumab PSD, July 2015). The PBAC maintained its view that, in UC, based upon available data, adalimumab is likely to be inferior to infliximab and a claim of non-inferiority cannot be justified.
- 7.7 The PBAC noted that the resubmission focused on improving access in rural and remote Australia as reflected in the consumer comments, and also estimated the distribution of adalimumab use in these areas should it become listed in the PBS for UC. The resubmission acknowledged that the availability of a subcutaneous preparation would grow the market by providing improved access to patients from rural and remote areas and those who may prefer a self-administered injection.
- 7.8 The PBAC noted that the resubmission offered a [REDACTED]% [REDACTED]. Given that inferiority (compared with infliximab) in the maintenance phase is also likely, there is no basis to accept the same price of infliximab. In the absence of a modelled economic evaluation of the cost savings per health outcome foregone, the PBAC considered that a reduction in price of adalimumab of around [REDACTED]% in the maintenance treatment phase is likely to be reasonable given the observed relative treatment effects in both phases and that this about [REDACTED] of the [REDACTED].
- 7.9 The PBAC noted that the resubmission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

AbbVie maintains that adalimumab offers an important treatment alternative in ulcerative colitis, and believes the data presented in its submission demonstrates non-inferiority of adalimumab in maintenance treatment of moderate to severe ulcerative colitis. The data included three randomised controlled trials comparing adalimumab to placebo, three RCTs comparing infliximab to placebo and three studies presenting real world evidence which demonstrate non-inferiority of adalimumab and infliximab. AbbVie understands that there is a significant unmet patient need for an alternative route of administration, and will continue to work with the PBAC to find a way forward.