7.02 ADALIMUMAB, 40 mg in 0.8 mL pre-filled syringe, 40 mg in 0.8 mL pre-filled pen, Humira®, Abbvie Pty Ltd

1 Purpose of Application

1.1 The minor re-submission sought an Authority Required listing for adalimumab for the initial treatment of moderate-to-severe hidradenitis suppurativa (HS) and Authority Required (STREAMLINED) listing for subsequent continuation of HS.

2 Requested listing

2.1 The minor re-submission requested the following restriction.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
ADALIMUMAB Injection, 40 mg in 0.8 mL pre-filled syringe Injection, 40 mg in 0.8 mL pre-filled pen	6	0	Effective price $[redacted] Public price $4,792.37	HUMIRA®	AbbVie Pty Ltd
ADALIMUMAB Injection, 40 mg in 0.8 mL pre-filled syringe Injection, 40 mg in 0.8 mL pre-filled pen	4	2	Effective price $[redacted] Public price $3,243.87	HUMIRA®	AbbVie Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Moderate to severe
Condition:	Hidradenitis suppurativa
PBS indication:	Moderate to severe hidradenitis suppurativa
Treatment phase:	Initial treatment (new patients)
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required – Telephone ☐ Authority Required – Emergency ☐ Authority Required – Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a dermatologist

Clinical criteria:	Patient must have confirmed hidradenitis suppurativa, with the diagnosis confirmed by a dermatologist; AND Patient must have failed to achieve an adequate response to 2 courses of different antibiotics each for 3 months; OR Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal or a medical contra-indication to such therapy; AND Patient must have, at the time of application, disease severity considered to be moderate to severe as demonstrated by a Hurley stage II or III with an AN count ≥3 preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior conventional treatment and which is no more than 1 month old at the time of application.
Prescriber Instructions	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 4 doses of 40 mg and 2 repeats. 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.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐ Midwives
Severity:	Moderate to severe
Condition:	Hidradenitis suppurativa
PBS indication:	Moderate to severe hidradenitis suppurativa
Treatment phase:	Re-initiation of PBS-subsidised treatment of hidradenitis suppurativa by a dermatologist
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☐Streamlined
Treatment criteria:	Must be treated by a dermatologist
Clinical criteria:	Patient must have a documented history of hidradenitis suppurativa, with the diagnosis confirmed by a dermatologist; AND Patient must have, an AN count ≥3 AND Patient has previously received PBS-subsidised adalimumab for the treatment hidradenitis suppurativa; and EITHER has demonstrated or sustained an adequate response to the most recent course of PBS-subsidised treatment with adalimumab for this condition; OR has failed to demonstrate or sustain an adequate response to PBS-subsidised treatment with adalimumab for this condition and 12 months have elapsed from the date on which treatment was ceased.
Prescriber Instructions	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 4 doses of 40 mg and 2 repeats. 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.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ADALIMUMAB Injection, 40 mg in 0.8 mL pre-filled syringe Injection, 40 mg in 0.8 mL pre-filled pen	4	5	Effective price $[redacted] Public price $3,243.87	HUMIRA® AbbVie Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Moderate to severe
Condition:	Hidradenitis suppurativa
PBS indication:	Moderate to severe hidradenitis suppurativa
Treatment phase:	Continuing treatment (initial)
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing Only ☐ Authority Required – Telephone ☐ Authority Required – Emergency ☐ Authority Required – Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a dermatologist
Clinical criteria:	Patient must have a documented history of moderate to severe hidradenitis suppurativa; AND Patient must have previously been issued with an initiation prescription for this drug for this condition; AND Patient must have demonstrated HiSCR with this drug, defined as a 50% decrease from baseline in inflammatory abscesses and nodules, with the assessment being no more than 1 month old at the time of application.
Prescriber Instructions	If the application is the first application for continuing treatment with adalimumab, HiSCR 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. The 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 the Department of Human Services 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 criterion. Where an assessment is not submitted to the Department of Human Services within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with this drug. Patients are eligible to receive an additional 24 weeks of treatment with this drug providing they demonstrate a response as described above. A maximum of 24 weeks treatment will be authorised under this criterion.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Moderate to severe
Condition:	Hidradenitis suppurativa
PBS indication:	Moderate to severe hidradenitis suppurativa

Treatment phase:	Continuing treatment (subsequent)
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing Only ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☒Streamlined
Treatment criteria:	Must be treated by a dermatologist
Clinical criteria:	Patient must have a documented history of moderate to severe hidradenitis suppurativa; AND Patient must have previously been issued with a prescription for this drug for this condition; AND Patient must have demonstrated an adequate response to treatment with this drug as defined as achieving HiSCR (50% reduction in AN count as compared to baseline with no increase in abscesses or draining fistulae) with the assessment being no more than 1 month old at the time of application.
Prescriber Instructions	If the application is the first application for continuing treatment after the initiation and 1st continuing script with adalimumab, an AN50 assessment of the patient's response to this initial course of treatment must be made following a minimum of 24 weeks of therapy after the initiation course, so that there is adequate time for a response to be demonstrated. The 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 the Department of Human Services 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 criterion. Where an assessment is not submitted to the Department of Human Services within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with this drug. Patients are eligible to receive continuing treatment with this drug 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.

2.2 The sponsor proposed that patients who do not respond according to HiSCR have a maximum of three attempts, 12 months apart, in order to achieve HiSCR. This was not incorporated in the requested listing. The pre-PBAC response proposed removing the re-treatment of patients who have failed to demonstrate response after one initiation script from the restriction criteria.

2.3 As recorded in the Public Summary Document (PSD) of the March 2016 PBAC meeting, the PBAC considered that a re-submission would need to present a well-defined place of adalimumab in the treatment algorithm for HS. The re-submission stated that the place of adalimumab in the treatment algorithm reflected the updated TGA wording, wherein patients who achieve HiSCR at 12 weeks are allowed to continue treatment. Patients are required to fail antibiotic treatment prior which is also in line with the updated TGA indication wording.

2.4 The TGA approved Product Information advised that adalimumab should be discontinued in patients without benefit after 12 weeks and that ongoing evidence of benefit, potential loss of response and the risks of treatment in patients continuing adalimumab beyond 12 weeks should be periodically evaluated "for example, after a further 12 weeks and every 6 months thereafter". The re-submission suggested re-evaluation every 24 weeks (6 months). This is similar to the suggested periods in the Product Information, but without the first re-evaluation after "a further 12 weeks".

2.5 The March 2016 pre-PBAC response and the minor re-submission requested listing for continuing therapy for HiSCR responders at week 12 (as opposed to partial responders based on AN25 as originally requested in the March 2016 major submission). The PBAC considered that this was reasonable and consistent with the ACPM recommendation (paragraph 7.4 of the March 2016 adalimumab PSD). The proposed restriction did not include a limit on the number of times a patient who has previously responded to treatment can be prescribed adalimumab for HS. The pre-PBAC response argued that responders may require a temporary break in therapy (e.g. desire to fall pregnant or have surgery) and these patients should be allowed to re-initiate treatment after this break. The pre-PBAC response stated that the number of responding patients that were expected to re-initiate treatment is estimated to be fewer than 5% of responding patients per year.

2.6 The pre-PBAC response for the current submission included a revised price offer of a [redacted]% discount on the published price of adalimumab.

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

3 Background

3.1 Adalimumab is TGA registered for the treatment of active moderate to severe HS in adult patients with an inadequate response to conventional systemic HS therapy.

3.2 A major submission for adalimumab for HS was rejected at the March 2016 PBAC meeting on the basis of unknown cost effectiveness of ongoing treatment with adalimumab (paragraph 7.1 of the March 2016 adalimumab PSD).

3.3 In March 2016, the PBAC considered that "a major re-submission should include a revised model of ongoing therapy with adalimumab and more conservative assumptions regarding the maintenance of treatment benefit. The re-submission would also need to present additional supportive evidence to justify the choice of the HiSCR primary outcome and have a well-defined place of adalimumab in the treatment algorithm for this condition. The utilisation and financial estimates should also be updated to reflect ongoing treatment" (paragraph 7.13 of the March 2016 adalimumab PSD).

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

4 Clinical place for the proposed therapy

4.1 HS is an inflammatory disease of the hair follicle associated with inflammatory cytokines including TNF-α and interleukins. HS is a chronic, inflammatory skin disease, with painful nodules causing morbidity and poor quality of life.

4.2 Adalimumab is proposed for patients with moderate-to-severe disease with an abscess and inflammatory nodule count greater or equal to 3, and prior treatment with 2 courses of antibiotics for at least 3 months duration each.

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

5 Comparator

5.1 The previous major submission considered by the PBAC in March 2016 nominated best supportive care (BSC) (placebo). This was unchanged in the minor re-submission. The PBAC considered that BSC was the appropriate comparator (paragraph 7.5 of the March 2016 adalimumab PSD).

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

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 an individual (1) and health care professionals (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adalimumab including the improvements in disease control and quality of life. The comments were supportive of a listing that restricted access to the most severely affected patients for whom other treatments have been ineffective or inappropriate.

Clinical trials

6.3 No new clinical data were presented in the minor re-submission. The March 2016 submission included three head-to-head trials comparing adalimumab to placebo: M10-467 (n=102), PIONEER I (n=307) and PIONEER II (n=326).

6.4 The minor re-submission sought to respecify the best estimate of the base case ICER by reducing the price and adapting the continuation criteria.

6.5 It was noted in the March 2016 adalimumab PSD that the primary outcome (HiSCR) had not been previously considered by the PBAC, was developed retrospectively using data from M10-467, does not capture all aspects of quality of life and is not as well established as other outcomes, such as PASI75 for chronic plaque psoriasis. The PBAC also considered that should the HiSCR outcome be used as an outcome measure, more supporting data would be required to justify the choice of using HiSCR as an outcome measure in this setting (paragraph 7.6 of the March 2016 adalimumab PSD). The minor re-submission reiterated that HiSCR is a validated and reliable outcome measure, which has been published in peer reviewed journals and accepted by respected regulatory agencies internationally.

6.6 The minor re-submission stated there is no additional data collection planned to assess the outstanding areas of concern addressed in the March 2016 adalimumab

PSD (i.e. the maintenance of treatment benefit in the longer term and with re-treatment).

Comparative effectiveness

6.7 The trial results remain unchanged from the major submission considered in March 2016. The results from the March 2016 submission are repeated below.

Table 1: HiSCR results across the direct randomised trials

Trial ID	HiSCR response at Week 12			
	ADA 40mg ew n/N (%)	Placebo n/N (%)	RD [95% CI]	RR[95% CI]
M10-467[a]	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]
Pooled result from random effects model			[redacted]	[redacted]
Chi-square (*Q*) for heterogeneity: *P* = I^2 statistic with 95% uncertainty interval = Test for overall effect: *P* =			[redacted] % [redacted]	[redacted] % < [redacted]
Pooled result from random effects model excluding study M10-467			[redacted]	[redacted]
Chi-square (*Q*) for heterogeneity: *P* = I^2 statistic with 95% uncertainty interval = Test for overall effect: *P* =			[redacted] % [redacted]	[redacted] % < [redacted]

Abbreviations: CI, confidence interval; ew, every week; HiSCR, Hidradenitis Suppurativa Clinical Response; RD, risk difference; RR, relative risk

[a]MiTT: Modified intention to treat analysis

Source: Table B.6.2, p.106 of the submission

6.8 It was noted in the March 2016 adalimumab PSD that the claim of superior comparative effectiveness was adequately supported by the data for the first 12 weeks of treatment but not for the maintenance of efficacy beyond 12 weeks of therapy. The PBAC considered results from Period B of the PIONEER trials (weeks 12 to 36) were highly uncertain because of the exploratory nature of the analysis and small patient numbers.

Comparative harms

6.9 The trial results remain unchanged from the previous major submission considered in March 2016. In the March 2016 adalimumab PSD, the PBAC noted that there were similar numbers of patients reported in both the adalimumab and BSC arms of the three trials experiencing any adverse events (AEs), treatment-emergent infections and AEs leading to discontinuations.

Clinical claim

6.10 The re-submission did not explicitly state a clinical claim. The clinical claim in the March 2016 submission was superior efficacy and inferior safety of adalimumab compared with BSC.

6.11 In March 2016, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data for the first 12 weeks of treatment. However, the PBAC noted that there was limited comparative data and no clear evidence of clinically meaningful maintenance of efficacy beyond 12 weeks of therapy.

6.12 With regards to the current submission, the PBAC reaffirmed that the claim of superior comparative effectiveness was adequately supported by the data for the first 12 weeks of treatment. The PBAC noted that the requested listing restricted continuing treatment to those patients who responded to adalimumab. The pre-PBAC response presented the new data from the open label extension (OLE) study (which was not completed in time for the original submission or the minor re submission) for up to 108 weeks of treatment for patients treated continuously with adalimumab. The pre-PBAC response stated that the data demonstrated the efficacy of continuous treatment with adalimumab where HiSCR was maintained for up to two years. The PBAC considered that the new OLE study results may provide additional evidence of maintenance of effectiveness of adalimumab treatment beyond 12 weeks, however, the PBAC noted that this study had not been evaluated. While the PBAC considered that the claim of superior comparative effectiveness may be reasonable beyond 12 weeks, the PBAC did not accept the extrapolation of the treatment benefit beyond treatment discontinuation modelled in the re-submission. The PBAC considered that the claim of inferior comparative safety was reasonable.

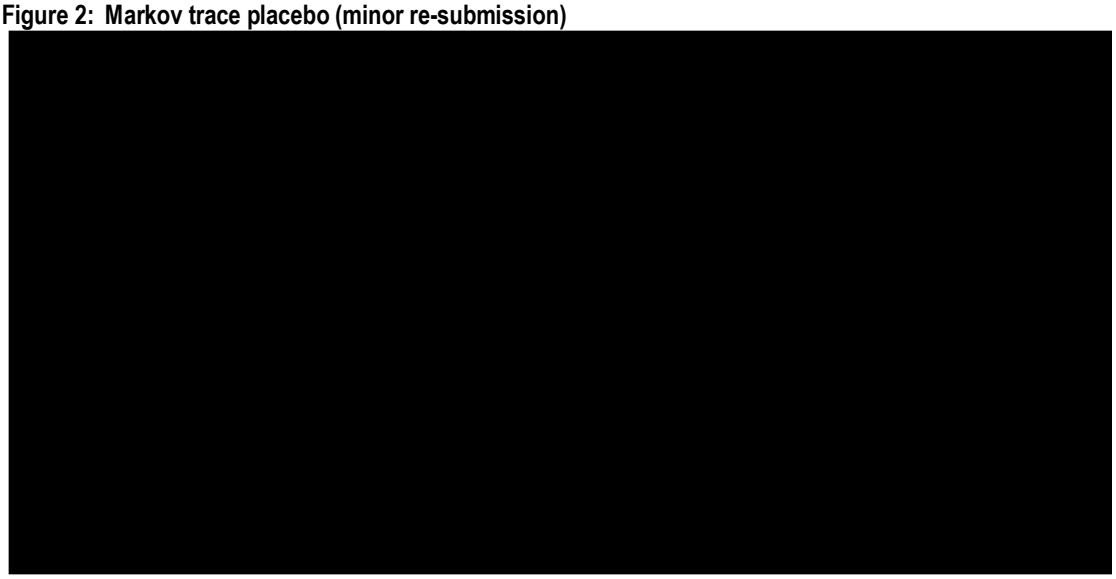
Economic analysis

6.13 In the major submission considered by the PBAC in March 2016, the sponsor presented a cost-effectiveness analysis against BSC. The minor re-submission sought to respecify the best estimate of the base case ICER by reducing the price. Furthermore, compared with the model in the March 2016 submission, changes were made to the continuation criteria, the assumed efficacy beyond 12 weeks, re-treatment post failure, prevalence, diagnosis rate and uptake. Further changes were made to the model in the pre-PBAC response including the removal of the re-treatment of non-responding patients in the restriction and model as well as a revised price.

6.14 The minor re-submission assumed convergence in the benefit for the treatment group to approach those in the placebo group (in a linear fashion) from week 36 to 20 years. The Markov traces obtained during the evaluation (see figures below) show that the number of patients in the health state “no response” after 20 years is equal between the treatment arms. While this approach assumed a diminishing benefit of adalimumab compared with placebo, it still assumes benefit after 36 weeks of therapy for a (gradually diminishing) proportion of patients, up to 20 years (without incurring treatment costs). This may overestimate the benefit of adalimumab compared with placebo. This was a more favourable assumption than in the March 2016 pre-PBAC commentary response, where convergence of benefit was assumed over a period of 10 years instead of 20 years.

Figure 1: Markov trace adalimumab, discontinued (minor re-submission)

Figure 2: Markov trace placebo (minor re-submission)



6.15 The March 2016 PSD noted (paragraph 7.10) that the economic model underestimated the cost of treatment as it assumed patients would not re-initiate treatment with adalimumab. This was considered inconsistent with the restriction requested in the submission for recommencement of treatment with adalimumab. The March 2016 pre-PBAC response and the minor re-submission addressed this issue by revising the economic model. In the revised model, [redacted]% of the discontinued patients were assumed to recommence treatment at week 60 and again at week 108. Recommencing patients were assumed to have the same transition probabilities as patients who continued adalimumab treatment from the beginning ("continuing patients").

6.16 The revised model in the minor re-submission likely underestimated the costs of re-treatments. The proportion of patients recommencing treatment ([redacted]%) was based on the proportion of HiSCR responses after re-treatment of non-responders in week 12 of the PIONEER studies. Thus a cost for adalimumab treatment was only applied

to [redacted]% of patients. This was not consistent with the financial projections which assumed all patients who failed treatment would recommence. The proposed listing allows **all** patients to recommence treatment after 12 months, with a minimum of 12 weeks of therapy before evaluation of response. Given this complexity, the pre-PBAC response proposed to remove the re-treatment of patients who failed to respond to treatment.

6.17 The proposed listing recommends evaluation of the response of recommencing patients following a minimum of 12 weeks of therapy. Since the revised model assumed that recommencing patients have the same transition probabilities as continuing patients, response evaluations for recommencing patients were assumed to take place at the same time points as response evaluations for continuing patients. Consequently, response evaluation of recommencing patients took place within one cycle (4 weeks) instead of after a minimum of 12 weeks. Therefore, most re-treated patients received only 4 weeks of treatment instead of a minimum of 12, resulting in underestimation of the costs.

6.18 The revised model assumed that recommencing patients have the same transition probabilities as continuing patients. Therefore, the probability of developing a response for patients recommencing treatment in week 60 was equal to the probability of developing a response for patients who were already treated since the beginning. This may underestimate treatment benefit since the probabilities of developing a response are lower in later treatment cycles. It may also overestimate treatment benefit in cases where patients who failed treatment in the past have a higher probability of failing treatment in the future. Given the model structure, the effect of alternative assumptions regarding the transition probabilities for recommencing patients could not be evaluated.

6.19 The probability of discontinuing treatment after recommencement (at 60 weeks and 108 weeks) was assumed to be the same as the probability of discontinuing treatment for patients receiving ongoing treatment from the start. This probability, [redacted]% per cycle, may be an underestimation for recommencing patients, since the probability of discontinuing treatment in the first 12 weeks was [redacted]% as opposed to [redacted]% per cycle. This may result in an overestimation of both costs and effects.

6.20 Table 2 provides the ICERs obtained from the various models over time, including the main differences between these models.

Table 2: ICERs produced by the models

Scenarios	Base case $/QALY
March 2016 submission Partial response at week 12 and HiSCR response at week 36 No price reduction 20 year time horizon Constant transition probabilities to extrapolate beyond 36 weeks No re-treatment post-failure No re-treatment post-success	[redacted]
March 2016 pre-PBAC response, revised base case HiSCR response at week 12 (decreases ICER) No price reduction 20 year time horizon Constant transition probabilities to extrapolate beyond 36 weeks No re-treatment post-failure No re-treatment post-success	[redacted]
March 2016 pre-PBAC commentary response, scenario HiSCR response at week 12 (decreases ICER) No price reduction 10 year time horizon (increases ICER) Convergence of benefit over 10 years (increases ICER) Re-treatment post-failure, at years 1 and 2 (increases ICER) No re-treatment post-success	[redacted]
July 2016 minor re-submission HiSCR response at week 12 (decreases ICER) Price reduction (decreases ICER) 20 year time horizon Convergence of benefit over 20 years (increases ICER) Re-treatment post-failure, at years 1 and 2 (increases ICER) No re-treatment post-success	[redacted][a]
July 2016 pre-PBAC response, revised base case (changes compared with July 2016 minor re-submission): Revised price offer No re-treatment post-failure	[redacted]
July 2016 pre-PBAC response, scenario (changes compared with July 2016 minor re-submission): Revised price offer No re-treatment post-failure 10 year time horizon Convergence of benefit over 10 years	[redacted]

Abbreviations: HiSCR, Hidradenitis Suppurativa Clinical Response; QALY, quality adjusted life year.

[a]This ICER is consistent with the DPMQs presented in Table 8 of the minor re-submission. It is inconsistent with the ICER presented in Table 7 of the minor re-submission ($45,000/QALY - $75,000 per QALY gained, consistent with a [redacted]% price reduction).

Source: Tables 5 and 7 from the minor re-submission, Table 2 from the pre-PBAC response and further supplemented during the evaluation.

The redacted table shows ICERs in the range of $15,000/QALY - $200,000/QALY.

6.21 In the minor re-submission, the transition probabilities for partial responders discontinuing after week 12 were taken from the adalimumab continuers, rather than the adalimumab discontinuers. Correcting this, the ICER increased from $45,000 - $75,000 to $45,000 - $75,000 per QALY gained.

6.22 The ICER presented in the minor re-submission ($45,000 - $75,000) is not consistent with the DPMQs presented in Table 8 of the minor re-submission. The ICER of

$45,000 – $75,000 is consistent with a [redacted]% reduction in the DPMQ of adalimumab. Table 8 of the current re-submission provided effective DPMQs of $[redacted] (6*40mg pack) and $[redacted] (2*40mg pack). Using these DPMQs results in an ICER of $45,000 - $75,000 instead of $45,000 - $75,000.

6.23 As per the original submission, the proposed listing in the re-submission allows for the recommencement of treatment for previous responders and non-responders with a limit on the number of courses of treatment for non-responders but no limit for previous responders. While the economic evaluation and financial estimates in the minor re-submission did include recommencement of treatment for non-responders (after a 12 month break), they did not include stop and recommencement of treatment for responders (e.g. "intermittent treatment", or re-treatment of flares). This was consistent with the PBAC PSD: "the PBAC was of the view that patients would be unlikely to cease treatment but would receive ongoing treatment because of the chronic nature of this condition" (paragraph 7.3 of the March 2016 adalimumab PSD). However, the original and revised models assumed that almost all patients would cease treatment by [redacted] but that the benefit of treatment would continue until 20 years (albeit now at a diminishing rate). The assumption that all patients cease treatment within [redacted] is inconsistent with the PBAC view that treatment is likely to be ongoing in practice and the assumption of the continuing benefit to 20 years is optimistic. Together, these assumptions would have significantly underestimated the ICER per QALY.

6.24 If patients are subsequently re-treated for future flares following an initial course of treatment in practice, rather than receiving ongoing therapy, then the time horizon is too long as the model does not capture the recurrent nature of the disease and recommencement of treatment. Previous models reviewed by the PBAC for biological treatments for other autoimmune conditions with fluctuating levels of disease activity (and recurrence) have had shorter time horizons. For example, a five year time horizon was used for ustekinumab for severe chronic plaque psoriasis (ustekinumab, PSD, November 2009) and a three year time horizon was used for infliximab for acute severe ulcerative colitis (infliximab, ulcerative colitis PSD, March 2013). The pre-PBAC response argued that a comparison of HS with ulcerative colitis is not clinically appropriate considering that ulcerative colitis is an acute condition, requiring treatment with infliximab for only six weeks. In this regard, a 10 year time horizon was used for infliximab for moderate to severe (chronic) ulcerative colitis (infliximab, PSD, March 2014).

6.25 If the time horizon and convergence of benefit period were reduced to 10 years, for example, the minor re-submission base case ICER increased to $75,000 - $105,000. Given the method used to converge the benefit to 10 years in the pre-PBAC model, it was not possible to calculate a similar figure for a 5 year period (however this would increase the ICER to beyond $75,000 - $105,000 per QALY).

6.26 The PBAC considered that if the uncertainties with the model were addressed, a basis for a PBAC recommendation for PBS listing for HS would require a price that produces an acceptable ICER. In this regard, the PBAC considered that an ICER in the range of $40,000 to $45,000 per QALY would be acceptable to enable adalimumab to be considered cost-effective for use in HS.

Drug cost/patient/year: $[redacted]

6.27 For 12 months of treatment: one initial prescription (4 weeks) for the induction script with an effective DPMQ of $[redacted] (6*40 mg) per script and 12 prescriptions (remaining 48 weeks) for the continuation scripts with $[redacted] (2*40 mg) per script. For 16 weeks (up to continuation one assessment) supply the drug cost per patient is $[redacted] which is one initial prescription $[redacted] and three prescriptions at $[redacted] each. These drug costs have not been updated to account for the revised price offer in the pre-PBAC response (see paragraph 2.6).

Estimated PBS usage & financial implications

6.28 The minor re-submission estimated a net cost to the PBS of $10 - $20 million in Year 5 of listing, with a total net cost to the PBS of $30 - $60 million over the first 5 years of listing. This is summarised in the table below as well as the expected patient/prescription numbers.

Table 3: Estimated use and financial implications using revised price offer

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number eligible	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6x40 mg pack (initial script)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 x (2x40 mg pack)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	NA	NA	NA	NA	NA
Estimated total net cost					
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS when the diagnosis rate is assumed to be 11.1%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 9 from the minor re-submission and supplemented during the evaluation.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million per year.

6.29 The estimates in Table 3 incorporate the adapted prevalence, diagnosis rate and uptake rate. Consistent with DUSC advice, uptake was increased (from [redacted]% to [redacted]%).

6.30 The diagnosis rate was decreased from [redacted]% (all years) in the original submission to [redacted]% (year 1) and increased to [redacted]% (year 5) in the pre-PBAC response and the minor re-submission. This change was not mentioned in the minor re-submission. These numbers were not verified because the source ("Final result, HS Epi study") was not available during the consideration of the minor re-submission. It was not clear how the diagnosis rate was obtained, to what extent the size and gradual increase were based on assumptions or measurement and if the sample size was large enough to be confident about these numbers. For each of the years, the

diagnosis rate in the minor re-submission is lower than the diagnosis rate in the original submission. This is inconsistent with DUSC advice. The PBAC agreed with DUSC that the diagnosis rate was likely to be underestimated in the original submission, so potentially further underestimated in the minor re-submission. Applying the diagnosis rate from the original submission ([redacted]%) results in substantially higher financial implications (see Table 3 above).

6.31 The financial projections included patients eligible to re-attempt treatment post-failure after a 12-month break. As opposed to [redacted]% in the economic evaluation, it was assumed that 100% of the patients would re-attempt treatment after a break. This may overestimate the number of adalimumab users since an unknown proportion of patients may not wish re-treatment. On the other hand, the financial projections did not include a second re-treatment despite the patients failing treatment in year one and three being eligible to start treatment again in year five. This may result in an underestimation of the costs.

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

7 PBAC Outcome

7.1 The PBAC did not recommend adalimumab for PBS listing for moderate to severe hidradenitis suppurativa (HS) on the basis of high and uncertain cost effectiveness.

7.2 Following the decision to reject the submission in March 2016, the PBAC considered that a major re-submission should include a revised model of ongoing therapy with adalimumab and more conservative assumptions regarding the maintenance of treatment benefit. In its consideration of the current submission, the PBAC noted that the minor re-submission requested the same restriction and presented the same model as the March 2016 pre-PBAC response with a reduced price offer. The PBAC further noted that the pre-PBAC response for the current submission removed the treatment of non-responders in the requested restriction and presented a revised price offer.

7.3 The PBAC noted that the continuation criteria require the patient to achieve at least a 50% HiSCR as per the ACPM recommendation. The PBAC considered that the continuing restriction should be Authority Required (in-writing) as per the requested initial restriction (as opposed to the requested STREAMLINED authority).

7.4 The PBAC reaffirmed that there is a high clinical need for an effective treatment for moderate to severe HS. The PBAC acknowledged the consumer comments received in relation to the submission, both from people living with the condition and on behalf of patients.

7.5 The PBAC recalled that it previously accepted BSC as the appropriate comparator.

7.6 The PBAC noted that no new clinical trial data were presented in the minor re-submission but that outcomes from the OLE study were provided in the pre-PBAC response. The pre-PBAC response stated that the OLE results demonstrated "the efficacy of adalimumab in terms of achievement of HiSCR for up to 2 years of

treatment". The PBAC noted that this was new evidence in the pre-PBAC response and that this had not been formally evaluated.

7.7 The PBAC recalled that the economic model in the March 2016 submission assumed an indefinite benefit with adalimumab (compared with BSC) following treatment cessation out to a 20-year time horizon, and that nearly all patients discontinue therapy within [redacted]. The March 2016 pre-PBAC response and current minor re-submission modelled a scenario with a gradually diminishing incremental benefit associated with adalimumab treatment such that at the end of the time horizon there was no additional benefit compared with placebo. The PBAC considered that while the approach in the minor re-submission was more conservative than the March 2016 submission, it still assumed a benefit for patients for up to 20 years while nearly all patients discontinue therapy within [redacted] (and therefore do not incur treatment costs while continuing to receive a benefit). Therefore, this approach may overestimate the benefit of adalimumab compared with placebo. The PBAC considered that while a 20-year time horizon may be appropriate in the context of a chronic condition like HS, it was inappropriate when assuming nearly all patients discontinue therapy within [redacted]. The PBAC noted some patients may be treated for long periods of time and the model did not reflect the reality of clinical practice. With further revision of the model the PBAC did not consider the requested listing to be sufficiently cost effective with the time horizon reduced to 10 years. The PBAC considered that given the chronic nature of the condition, it was likely that patients would receive longer-term treatment with adalimumab (as opposed to discontinuing treatment within [redacted]) and expressed a preference for a model that modelled the cost effectiveness of this scenario. In this case, a longer time horizon could be considered more reasonable.

7.8 In addition, the PBAC noted the other issues with the economic model raised in paragraphs 6.15 to 6.24 remained concerns that should be addressed in any resubmission.

7.9 The PBAC noted the changes to the prevalence and uptake rate made in the March 2016 pre-PBAC response (which were unchanged in the minor re-submission), as per the March 2016 DUSC advice. The PBAC noted that the financial estimates would require updating to incorporate the diagnosis rate in the original submission and the DUSC advice ([redacted]%), revised price proposal and the removal of re-treatment of non-responders.

7.10 The PBAC considered that a major re-submission should include (but not be limited to):

- revised restriction criteria which include the removal of re-treatment for non-responders as proposed in the pre-PBAC response, as well as wording clarifying the re-treatment of responders who re-initiate treatment after a treatment break;
- the OLE study results for evaluation;
- a revised economic model with more conservative assumptions regarding the incremental benefit of adalimumab following treatment cessation (or, alternatively, a shorter time horizon) and addressing the other issues raised in paragraphs 6.15 to 6.24; and

- revised utilisation and financial estimates incorporating the [redacted]% diagnosis rate, changes to the requested restriction and price.

7.11 The PBAC noted that this submission 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

The Sponsor is disappointed with the PBAC's decision. AbbVie will continue to work towards ensuring adalimumab is made available as a reimbursed therapy for the treatment of this debilitating disease.