6.01 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 To request 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 adalimumab.

2 Requested listing

2.1 An abbreviated version of the requested restriction is below. Should the listing of adalimumab be recommended for the requested indication, the restriction will need to be developed in consultation with the RWG, DHS and the sponsor.

Initial treatment:

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

Authority required

Continuing treatment (first continuation and subsequent continuation):

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

Authority required (first continuation) and Streamlined (subsequent continuation)

2.2 The PBAC should consider if the use of an AN25 (at least a partial response) is appropriate for the 12-16 week continuation criteria given the limited data supporting its use and that the analysis was defined post-hoc (Section B.6 of the submission). In the PIONEER I and II trial, the primary outcome measured at week 12 was hidradenitis suppurativa clinical response (HiSCR). Patients were re-randomised for

entry into Period B (Week 13 to Week 36), this was not contingent on achieving HiSCR in Period A (Week 0 to Week 12).

2.3 There was limited experience in how adalimumab would be used in clinical practice over the long term.

2.4 The ESC noted that the restriction was complicated and the continuation criteria are difficult to justify.

2.5 The pre-PBAC response modified the requested restriction wording to include continuation criteria of HiSCR at 12 weeks arguing that this would reflect the population in which adalimumab is the most cost-effective and where the clinical data offer the greatest certainty of benefit.

2.6 The requested basis for listing was cost-effectiveness compared with best supportive care (BSC).

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

3 Background

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. At the time of the evaluation, the TGA Clinical Evaluation Report (CER) was available. The TGA Delegate Summary was available at the time of the ESC meeting. The ESC noted the indication that the TGA is likely to approve had changed since the evaluation was conducted. The CER recommended approval for 12 weeks of adalimumab but not for ongoing maintenance, while the Delegate's Summary suggested that maintenance therapy may be appropriate for responders at week 12.

3.2 The ACPM resolution was received subsequent to the ESC meeting. The ACPM resolved to recommend to the TGA Delegate that adalimumab has an overall positive benefit-risk profile for a revised indication. The revised indication limits the use of adalimumab as second line therapy to HS adult patients with an inadequate response to convention HS therapy. Whereas, the originally proposed indication was for the treatment of active moderate to severe HS in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscess and draining fistulas.

3.3 The ACPM also advised that use beyond 12 weeks should be contingent on evidence of benefit. The ACPM concurred with the TGA clinical evaluator that 'Ongoing use should be only in those with ≥ 50% reduction from baseline in total abscess and inflammatory nodule (AN) count, with no observed increase in either abscess or draining fistula counts at week 12, week 24 and every 6 months thereafter.'

3.4 Adalimumab for hidradenitis suppurativa had not been previously considered by the PBAC.

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

4 Clinical place for the proposed therapy

4.1 Hidradenitis Suppurativa is an inflammatory disease of the hair follicle associated with inflammatory cytokines including TNF-α and interleukins. HS is a chronic, inflammatory and 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 abscesses 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 Best supportive care (placebo). The ESC considered this was the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (7), and health care professionals (16) via the Consumer Comments facility on the PBS website. The comments described a high clinical need for more treatment options for this condition and a range of benefits of treatment with adalimumab including reduction in lesion inflammation and count and the associated improvement in quality of life.

Clinical trials

6.3 The submission was based on three head-to-head trials comparing adalimumab to placebo, M10-467 (n=102), PIONEER I (n=307) and PIONEER II (n=326).

6.4 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
M10-467	Trial report M10-467. A phase 2, multicentre study of the safety and efficacy of adalimumab in subjects with moderate to severe chronic hidradenitis suppurativa.	22 April 2009
	Kimball et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomised trial.	*Ann Intern Med* 2012;157(2):846-55
	Kimball et al. Efficacy and safety of adalimumab in treatment of moderate to severe hidradenitis suppurativa: results from the placebo-controlled portion of a phase II, randomised, double-blind study.	*J Am Acad Dermatol* 2011; 64(2 Suppl 1):AB155.
	Gottlieb et al. Efficacy and safety of adalimumab treatment in women with moderate to severe hidradenitis suppurativa: Analysis from the placebo-controlled portion of a phase II, randomised, double-blind study.	*Int J Gyneacol Obstet* 2012;119: S360.
	Kimball et al. Adalimumab reduces pain in patients with hidradenitis suppurativa: Results from a placebo-controlled phase II trial.	*J Am Acad Dermatol* 2012; 66(4 Suppl 1):AB42.
	Kimball et al Efficacy and safety of adalimumab for moderate to severe hidradenitis suppurativa: Results from the open-label phase of a 52-week phase II, randomised, study	*J Am Acad Dermatol* 2012; 66(4 Suppl 1):AB50.
	Mrowietz et al. Adalimumab improves health-related quality of life and work productivity in patients with hidradenitis suppurativa: Results from a placebo-controlled phase II trial.	*J Am Acad Dermatol* 2012; 66(4 Suppl 1):AB42.
	Zouboulis et al. High-sensitivity C-reactive protein response to adalimumab in hidradenitis suppurativa patients.	*J Invest Dermatol* 2012;132: S67.
	Zouboulis et al. Impact of weight and body mass index on high-sensitivity C-reactive protein response to adalimumab in hidradenitis suppurativa patients.	*J Am Acad Dermatol* 2012;66(4 Suppl 1):AB53.
	Gottlieb et al. Efficacy and safety of adalimumab treatment in women with moderate to severe hidradenitis suppurativa: Analysis from the placebo-controlled portion of a phase II, randomised, double-blind study.	*J Am Acad Dermatol* 2013;68(4 Suppl 1):AB49.
	Scheinfeld et al. Adalimumab treatment is associated with pain reduction in patients with hidradenitis suppurativa, regardless of the presence of depression: Results from a phase II, randomised, placebo-controlled trial. .	*J Am Acad Dermatol* 2014;70(5):AB35.
PIONEER I (M11-313)	Trial report M11-313. A phase 3 multicenter study of the safety and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa – PIONEER I. Trial report M12-555. A phase 3 open-label study of the safety and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa – PIONEER (open-label extension).	29 November 2011
	Armstrong et al. HUMIRA Improves Health-Related Quality of Life (HRQoL) in patients with moderate to severe Hidradenitis Suppurativa (HS): Results from the first 12 weeks of PIONEER I.	*J Invest Dermatol* 2014;134:S34.
	Jemec et al. Adalimumab improves treatment satisfaction with medication (TS-M) in patients with moderate to severe Hidradenitis Suppurativa (HS) in a 12-week randomised controlled trial (PIONEER I).	*J Invest Dermatol* 2014;134:S31.
	Kimball et al. Safety and efficacy of adalimumab in patients with	*J Invest Dermatol*

Trial ID	Protocol title/ Publication title	Publication citation
	moderate to severe hidradenitis suppurativa: Results from first 12 Weeks of PIONEER I, a Phase 3, Randomised, placebo - controlled trial. Herra et al. Safety and efficacy of Adalimumab in patients with moderate to severe hidradenitis suppurativa: results from first 12 weeks of PIONEER I, a phase 3, randomised, placebo - controlled trial. Kimball et al. Safety and efficacy of adalimumab in patients with moderate to severe hidradenitis suppurativa: Results from first 12 weeks of PIONEER I, a phase 3, randomised, placebo - controlled trial.	2015;134:S36. *Aust J Dermatol* 2015 56:34-35. *J Am Acad Dermatol* 2015 72(5):AB60.
PIONEER II (M11-810)	Trial report M11-810. A phase 3 multicenter study of the safety and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa – PIONEER II. Trial report M12-555. A phase 3 open-label study of the safety and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa – PIONEER (open-label extension). Jemec et al. Efficacy and safety of adalimumab in patients with moderate to severe hidradenitis suppurativa: Results from PIONEER II, a phase 3, randomised, placebo - controlled trial Hera et al. Efficacy and safety of Adalimumab in patients with moderate to severe hidradenitis suppurativa: results from PIONEER II, a phase 3 randomised placebo - controlled trial. Jemec et al. Adalimumab improves treatment satisfaction with medication (TS-M) in patients with moderate to severe hidradenitis suppurativa (HS) in a 12-week randomised controlled trial (PIONEER II).	28 December 2011 *J Am Acad Dermatol* 2014 72(5):AB45. *Aust J Dermatol* 2015;56:34-35. *J Am Acad Dermatol* 2015;72(5):AB39.

Source: Table B.2.2, p64-65 of the submission

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Adalimumab vs. placebo						
M10-467	102	R, DB, 16 weeks	Low	Hurley Stage I,II,III	HS-PGA score at week 16	Not used
PIONEER I	307	R, DB, 36 weeks	Low	Hurley Stage II and III	HiSCR at Week 12	Used
PIONEER II	326	R, OL, 36 weeks	Low	Hurley Stage II and III	HiSCR at Week 12	Used

DB=double blind; HS-PGA; hidradenitis suppurativa physician global assessment; HiSCR=hidradenitis suppurativa clinical response; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: compiled during the evaluation

6.6 Hidradenitis Suppurativa Clinical Response (HiSCR), the primary outcome in the PIONEER trials, measures inflammatory signs and symptoms of HS but does not capture all aspects of quality of life. HiSCR is defined as a ≥ 50% reduction in inflammatory lesions count (sum of abscesses and inflammatory nodules, AN), and no increase in abscesses or draining fistulas in HS when compared to baseline. HiSCR has not been previously considered by the PBAC. This outcome was developed retrospectively using data from M10-467. The PSCR (p2) argued that HiSCR is similar to tools used in the assessment of other inflammatory skin conditions such as PASI75 in chronic plaque psoriasis.

6.7 For M10-467, the main analysis presented in the submission was a post hoc analysis of outcomes using a modified ITT population. This was done in order for the results to be comparable with those for the PIONEER studies. The submission presented the pooled results of the primary outcome (and some secondary outcomes) with and without M10-467.

6.8 Results from Period B of the PIONEER trials (Week 12 to Week 36) should be interpreted with caution due to the exploratory nature of the analysis and small patient numbers.

6.9 The ESC noted that the trial participants were representative of the known epidemiology of HS (more common in young women, high BMI and smokers) (CER p27, 38). In noting that the adalimumab and placebo groups had similar HiSCR rates for the sub-group of patients with a BMI over 40 (CER p28), the ESC questioned whether a larger dose than that proposed by the submission would be required for a sub-group of obese patients.

Comparative effectiveness

6.10 There was a high placebo response rate in the PIONEER trials, [redacted]% [redacted]in PIONEER I and [redacted]% [redacted]in PIONEER II. The submission stated that the response rate seen in the placebo arms of the PIONEER studies can be attributed to the clinical trial setting whereby patients experience an improved standard of clinical management (including wound care) and therefore, a better outcome.

Table 3: Results of HiSCR 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] [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] [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

6.11 For the PIONEER trials, post-hoc analyses were undertaken based on 12 week HiSCR response.

- Of the [redacted] patients <u>who achieved a HiSCR at week 12</u>, [redacted] ([redacted]%) maintained a HiSCR at week 36 with continuing adalimumab treatment in Period B. This compared with [redacted]% ([redacted]/[redacted]) at Week 36 for patients who switched to placebo in Period B.
- Of the [redacted]patients <u>who did not achieve a HiSCR at week 12</u>, [redacted]([redacted]%) achieved a HiSCR at week 36 with continuing adalimumab treatment in Period B. This

compared with [redacted]% ([redacted]/[redacted]) at Week 36 for patients who switched to placebo in Period B.

Comparative harms

6.12 For the induction trial period (12 weeks or 16 weeks for M10-467), pooled across the three trials:

- A similar proportion of subjects in the adalimumab every week and placebo arms reported any adverse event ([redacted] versus [redacted]).
- A similar proportion of subjects in the adalimumab every week and placebo arms reported treatment-emergent infections ([redacted] versus [redacted]).
- A similar proportion of subjects in the adalimumab every week and placebo arms reported AEs leading to discontinuations ([redacted]).

Benefits/harms

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

Table 4: Summary of comparative benefits and harms for adalimumab and PBO

Trial	ADA	PBO	RD (95% CI)	RR (95% CI)
Benefits				
HiSCR response at Week 12				
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 RR 2.07 [redacted]			and RD [redacted]	
Pooled result from random effects model excluding M10-467 RR [redacted]			and RD [redacted]	
Harms				

	ADA	PBO	RD (95% CI)	Event rate/100 patients*		RR (95% CI)
				ADA	PBO	
Any adverse event						
M10-467	36/51	30/51	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]	66.9	[redacted]
AE leading to discontinuation						
M10-467	[redacted]	0/51	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Maximum duration of exposure: M10-467 = 16 weeks; PIONEER I = 12 weeks; PIONEER II = 12 weeks

[a] MiTT: Modified intention to treat analysis

Abbreviations: ADA = adalimumab; PBO = placebo; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation, RD (95% CI) and RR(95% CI) were calculated during the evaluation for each trial using RevMan.

6.14 On the basis of direct randomised evidence presented by the submission, for every 100 patients treated with adalimumab in comparison to placebo:

- Approximately [redacted] additional patients would have achieved HiSCR over a maximum duration of exposure of 12 weeks.

Clinical claim

6.15 The submission described adalimumab as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo (best supportive care).

- The ESC considered that the efficacy claim was adequately supported for 12 weeks of treatment. However, this was based on the HiSCR outcome and this outcome has not previously been considered by the PBAC.
    - At week 12, there were statistically significant improvements (PIONEER I and II analysis only) in only one of the three ranked secondary outcomes (modified Sartorius score, but not in abscesses and inflammatory nodule (AN) count of 0, 1 or 2, or skin pain (NRS30)).
    - There were statistically significant improvements (PIONEER I and II analysis only) in other secondary outcomes (proportion achieved AN50, AN75 and AN100; complete elimination of inflammatory nodules (but not abscesses or draining fistulas), proportion with flares, and number of days on flare).
    - There were statistically significant improvements in DLQI (PIONEER I and II), physical component score of the SF-36 (PIONEER I) and EQ-5D (PIONEER II).
- The ESC considered that the benefit of adalimumab treatment beyond week 12 was not supported in the submission. There was limited comparative data and no clear evidence of a clinically meaningful maintenance of efficacy beyond 12 weeks of therapy.
    - The TGA clinical evaluator recommended approval for 12 weeks of adalimumab but not for ongoing maintenance.
    - The evaluation considered that there was limited comparative data and no clear evidence of a clinically meaningful benefit of adalimumab maintenance therapy beyond 12 weeks. The PSCR (p1) argued that data from Period B of the PIONEER trials should be combined with data from the open label extension study M12 555 (Week 0-48) to assess the benefit of adalimumab maintenance therapy beyond 12 weeks. This data was provided to the TGA in response to the Clinical Evaluation Report.
    - The ESC noted that the TGA Delegate's Overview (provided subsequent to the evaluation) considered that there is evidence that responders at week 12 may maintain a benefit with ongoing weekly treatment. The Delegate's Overview considered that evidence of ongoing efficacy is strongest to week 36. But in patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.
    - No clinical evidence was provided assessing the efficacy of adalimumab when recommenced in responders or non-responders. The PSCR (p2) presented data for patients in Study M12-555 who received 12 weeks treatment with adalimumab every week (EW), followed by 12 weeks of placebo and a subsequent 12 weeks of EW to argue that patients who cease ADA therapy regain response upon recommencement. The ESC considered that the reasons patients discontinued treatment in the trial are likely to differ from those for discontinuing treatment in clinical practice and hence the efficacy of adalimumab treatment in patients re-commencing treatment is uncertain.
- The ESC considered that the inferiority claim for safety was reasonable.

6.16 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 a clinically meaningful maintenance of efficacy beyond 12 weeks of therapy.

6.17 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.18 The re-submission presented a modelled cost utility analysis.

Table 5: Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 36 weeks in the trials
Outcomes	QALYs
Methods used to generate results	Cohort expected value analysis
Health states	High response, Response, Partial Response, No Response and Dead
Cycle length	Based on selected key time-points in PIONEER I and PIONEER II: First cycle (Week 0 to Week 2): 2 weeks Second cycle (Week 2 to Week 4): 2 weeks Third cycle onwards (Week 4 onwards): 4 weeks
Transition probabilities	For Week 0-36: Pooled results from PIONEER I and II for week 0-36 (Section C.3.1) For beyond Week 36: modelled using data from Period B (Week 12-36) of PIONEER I and II using generalised logit model (Section C.2.1). Transitions for patients continuing ADA: based on n=70; transitions for patients discontinuing ADA: based on n=27; transitions for patients treated with BSC: n=151

Source: compiled during the evaluation

Table 6: Key drivers of the model

Description	Method/Value	Impact
Time horizon	20 years; assumed from 36 week trial duration	High, favours adalimumab
Transition probabilities beyond Week 36	Modelled from Period B of PIONEER trials using subgroups. Based on the distribution across the health states in the model from 1.53 years onwards: • For patients who discontinue adalimumab treatment, approximately [redacted]% have a response for the remaining model duration ([redacted]% high response, [redacted]% response and [redacted]% partial response); and • For patients who are treated with BSC, approximately [redacted]% having a response for the remaining model duration ([redacted]% high response, [redacted]% response and [redacted]% partial response).	High, favours adalimumab
Health state costs for medical resource use	High response: $[redacted]; Response: $[redacted]; Partial response: $[redacted]; No response: $[redacted] In the model, due to being in worse health states, the healthcare costs for treating HS (excluding adalimumab) are higher for the BSC arm compared with the adalimumab arm.	High, favours adalimumab

Source: compiled during the evaluation

Table 7: Results of the stepped economic evaluation

Step and component	Adalimumab	Placebo	Increment
Step 1: trial-based costs and outcomes			
Costs	$[redacted]	$0	$[redacted]
HiSCR	[redacted]	[redacted]	[redacted]
Incremental cost/additional HiSCR at Week 12			**$[redacted]**
Step 2: modelled evaluation (cost per HiSCR response, 12 weeks, undiscounted)			
Costs	$[redacted]	$0	$[redacted]
HiSCR	[redacted]	[redacted]	[redacted]
Incremental cost/ additional HiSCR at Week 12			**$[redacted]**
Step 3: modelled evaluation (QALYs, 36 weeks, undiscounted)			
Costs	*$[redacted]*	*$4,698*	*$[redacted]*[a]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**
Step 4: modelled evaluation (QALYs, 20 years, discounted)			
Costs	$[redacted]	$98,510	$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**

[a] *The submission stated that the incremental cost was $[redacted], however, this is for adalimumab drug cost only and not disease cost*

Abbreviations: HiSCR, hidradenitis suppurativa clinical response

Source: Section D.5 of the submission and constructed during the evaluation

6.19 The major driver of the model was the time horizon. Constant transition probabilities were used to extrapolate the clinical data beyond 36 weeks up to 20 years. In the submission, the time horizon was reduced to 10 years and this increased the ICER to $45,000 - $75,000 per QALY gained. With a time horizon of 12 weeks (the duration of treatment recommended by the TGA Clinical Evaluator) the ICER increased to more than $200,000/QALY. The ESC noted that while the TGA Delegate subsequently supported maintenance treatment beyond 12 weeks in responding patients, the model remained highly sensitive to the choice of the time horizon.

- The PSCR (pg 4) argued that a 20 year time horizon was appropriate as HS is a chronic disease.
- The ESC acknowledged the chronic nature of HS but considered that the benefit of treatment with adalimumab would be unlikely to continue for 20 years. The ESC considered that the submission failed to recognise the limitations in the data presented and the inherent uncertainties in the extrapolation of 12 to 36 week data to a 20-year model.

6.20 The reduced ICER with a longer time horizon reflected that over time patients discontinue treatment with adalimumab (and hence there is no associated cost) but the benefit of treatment is maintained (in terms of lower costs for the underlying treatment of HS and a higher utility value). In the model, nearly all patients (>99%) discontinued adalimumab treatment by [redacted] years and hence for the majority of the modelled time horizon, no adalimumab costs are applied but there is a benefit (compared with BSC) associated with prior adalimumab treatment. Specifically, from 1.53 years onwards, approximately [redacted]% of patients who discontinued adalimumab treatment had a response ([redacted]% high response, [redacted]% response and [redacted]% partial response) compared with approximately [redacted]% of patients treated with BSC ([redacted]% high response, [redacted]% response and [redacted]% partial response).

- The PSCR (p4) argued that this assumption was not unreasonable as one of the reasons a patient may discontinue adalimumab would be that patients achieve long-term control of the symptoms and adverse effects of HS and that there may

be ongoing benefit from previous adalimumab treatment due to generalised suppression of the immune system. The PSCR presented a sensitivity analysis which modelled a gradual diminishing benefit for patients who had discontinued adalimumab treatment such that at 20 years there was no additional benefit compared with placebo (ICER of $75,000/QALY - $105,000/QALY saved).

- The ESC noted that this analysis still assumed benefit from previous treatment with adalimumab without incurring any treatment costs. The model inputs were not provided and hence the ICER could not be verified.
- Furthermore, the ESC considered that the argument did not address uncertainties in extrapolating data from 36 weeks to 20 years, and that the ICER would be considerably higher if the same benefit was assumed in the convergence approach for a shorter time horizon model.

6.21 The cost of adalimumab treatment is $[redacted]. There are additional costs for AEs ($[redacted]) and treatment initiation ($[redacted]). Thus the total cost of adalimumab treatment is $[redacted]. There is a cost-offset of $[redacted] as a result of adalimumab treated patients being in better response states. Thus the incremental cost with adalimumab treatment is $[redacted] (undiscounted). The adalimumab drug cost accrues over the initial [redacted] years of the model (as essentially all patients have discontinued treatment by [redacted] years). The cost offset accrues over the 20 year model time horizon (as a higher proportion of patients treated with adalimumab remain in response states compared with BSC).

6.22 The ESC considered that the modelled costs were underestimated as no patients re-initiate treatment with adalimumab in the model. This was inconsistent with the requested restriction.

- The PSCR (p4-5) argued that while the intermittent nature of disease is not captured, it can be assumed that 'the cost-effectiveness of each course of treatment will be similar to that of initial treatment'.
- The ESC considered this assumption was highly optimistic and with no supporting data provided. In addition, in light of the sponsor arguing for a 20 year time horizon, it would not be reasonable to apply the 20-year ICER to each course of treatment. If a similar ICER was to apply to each episode of treatment, then it would be more appropriate to use a much shorter time horizon (i.e. a time horizon that reflects the duration of an episode of flare up).

6.23 The pre-PBAC response presented sensitivity analyses for the following scenarios (and combinations of these scenarios) at three price points (the requested price and [redacted]% and [redacted]% less than the requested price):

- 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;
- 10 year time horizon;
- re-treatment allowed at years 1 and 2.

Drug cost/patient/year: $[redacted]

6.24 For 12 months of treatment: an initial prescription (4 weeks of treatment) with an effective DPMQ of $[redacted](6 x 40 mg injections per script) and 12 prescriptions (remaining 48 weeks) for the continuing treatment with an effective DPMQ of $[redacted] (2 x 40 mg injections per script).

6.25 For 16 weeks of treatment (up to the first continuation assessment): $[redacted] per patient based on 1 initial prescription ($[redacted]) and 3 continuation prescriptions ($[redacted] per script).

Estimated PBS usage & financial implications

6.26 The submission was considered by DUSC.

6.27 The financial implications were estimated using an epidemiological approach. The prevalence of HS of [redacted]% ([redacted] out of [redacted] participants) was based on interim Australian data.

Table 8: Estimated use and financial implications

	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]

[a] Assuming 1 script per 6*40 mg pack and 12 scripts of 2*(2*40 mg) pack year as estimated by the submission.
Source: Table E.2-2 and Table E.2-3, p.190, Table E.2.8, p.194 and Table E.2.12, p.196 of the submission

The redacted table above shows that at year 5, the estimated number of patients would be less than 10,000 and the net cost to PBS would be $10-$20 million.

6.28 In Year 5 the submission assumed that [redacted]% ([redacted] out of [redacted]) of diagnosed HS patients would be treated with adalimumab. This was based on [redacted]% ([redacted]) patients with HS being diagnosed and an uptake rate of [redacted]%.

6.29 The DUSC considered that the main issue in the estimates presented in the submission was that the number of patients who will be treated with adalimumab was underestimated, mainly due to:

- Underestimation of the uptake rate. Uptake is expected to be higher than [redacted]% in Year 1 with likely rapid uptake of a drug clinicians are familiar with in patients diagnosed with HS who currently have limited evidence based treatment options. Uptake is also expected to be higher than estimated in subsequent years, though gradual in increase.
- Likely underestimation of the diagnosis rate, particularly in later years, as general practitioners increasingly refer patients to specialists as awareness of an additional treatment option grows.

6.30 The DUSC considered the prevalence estimate of [redacted]% of the Australian adult population, updated to [redacted]% in the PSCR (PSCR pg. 5) from the completed epidemiological study results, provided a reasonable estimate of the prevalence of hidradenitis suppurativa in the Australian population.

6.30 The DUSC noted that the estimated diagnosis rate of [redacted]% was obtained from the small sample size of three participants diagnosed out of [redacted] suspected to have HS from the epidemiological study.

Quality Use of Medicines

6.32 The DUSC noted the importance of smoking cessation, weight reduction and good hygiene in the management of HS.

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 unknown cost effectiveness of ongoing treatment with adalimumab.

7.2 The PBAC acknowledged there is a high clinical need for an effective treatment for moderate to severe HS. The chronic nature of the inflammatory skin disease causes significant morbidity and poor quality of life. The PBAC acknowledged the consumer comments received in relation to the submission, both from people living with the condition and on behalf of patients.

7.3 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.

7.4 The PBAC noted the pre-PBAC response changed the requested listing to limit continuing therapy to HiSCR responders at week 12 (defined as ≥ 50% decrease from baseline in inflammatory abscesses and nodules and no increase in the numbers of abscesses or draining fistulae, AN50), rather than partial responders based on AN25 as originally proposed (followed by a requirement for HiSCR at week 36). The PBAC considered that was reasonable and consistent with the ACPM recommendation that 'Ongoing use should be only in those with ≥ 50% reduction from baseline in total abscess and inflammatory nodule (AN) count, with no observed increase in either abscess or draining fistula counts at week 12, week 24 and every 6 months thereafter.'

7.5 The PBAC considered that BSC was the appropriate comparator.

7.6 The PBAC noted that three head-to-head trials M10-467 (n=102), PIONEER (n=307) and PIONEER II (n=326) were presented. The primary outcome in the PIONEER trials was HiSCR while the main analysis presented for M10-467 was a post-hoc analysis of outcomes using a modified ITT population in order for the results to be comparable with those in the PIONEER trials. The PBAC noted that it had not previously considered a submission that included the primary outcome measure, HiSCR. The PBAC agreed with ESC that this outcome only measures inflammatory signs and symptoms of the condition but does not capture all aspects of quality of life. The PBAC noted that this outcome measure 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.

7.7 The PBAC noted there were high placebo response rates in the PIONEER trials ([redacted]% in PIONEER I and [redacted]% in PIONEER II compared with [redacted]% and [redacted]% in adalimumab treatment groups, respectively) which may have been due to an improved standard of clinical management in the trial. The PBAC noted that the pooled result from all three trials indicated that for every 100 patients treated with adalimumab in comparison to placebo, approximately [redacted] additional patients would have achieved HiSCR over a maximum duration of exposure of 12 weeks. The PBAC therefore considered that the submission's claim of superior comparative effectiveness (compared with BSC) based on the HiSCR outcome was adequately supported by the data for the first 12 weeks of treatment.

7.8 The PBAC noted that that there was limited comparative data and no clear evidence of a clinically meaningful 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.

7.9 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 categories. The PBAC considered that the submission's claim of inferior safety was reasonable.

7.10 The PBAC noted that the time horizon was the major driver of the model in the presented cost-utility analysis. In the submission, when the time horizon was reduced from 20 years to 10 years the ICER increased from $15,000/QALY - $45,000/QALY to $45,000/QALY - $75,000/QALY and a further reduction of the time horizon to 12 weeks increased the ICER to more than $200,000/QALY. The PBAC noted that the ICER increased for shorter time horizons due to the assumptions that nearly all patients discontinued adalimumab treatment by [redacted] years but the benefit of treatment was maintained through to 20 years. The pre-PBAC response argued that a 20 year time horizon was appropriate as HS is a chronic disease. The PBAC acknowledged the chronic nature of the condition but considered that it was highly uncertain for the model to assume an indefinite continuing benefit with adalimumab following cessation of therapy. The PBAC further noted that the 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.

7.11 The PBAC noted that the pre-PBAC response presented a revised model based on the revised requested restriction to allow only patients who are HiSCR responders to continue treatment beyond 12 weeks. The PBAC further noted the additional sensitivity analyses including convergence of the benefit of adalimumab between week 36 and 20 years, a shorter time horizon (10 years) and re-treatment at Year 1 and 2 for non-responders.

7.12 The PBAC agreed with DUSC that the uptake rate and the diagnosis rate were likely to be underestimated by the submission. The PBAC considered that utilisation in Year 1 would be expected to be higher than [redacted]% as dermatologists are already familiar with prescribing adalimumab and because of the lack of other evidence-

based and subsidised treatments for this condition. The PBAC considered that more general practitioners would refer patients to specialists for treatment with adalimumab as awareness of an additional treatment option for HS increased. The PBAC noted that revised financial estimates were presented in the pre-PBAC response with a prevalence rate of [redacted]%, a decreased diagnosis rate of [redacted]% in year 1 to [redacted]% year 5, an increased uptake rate of [redacted]% across each of the first years, a decreased continuation rate of [redacted]% at 12 weeks and an increased subsequent continuation rate of [redacted]%.

7.13 The PBAC considered that there is a clinical need for subsidised access to adalimumab for HS and would welcome a major resubmission. The PBAC considered that a major resubmission should include a revised model of ongoing therapy with adalimumab and more conservative assumptions regarding the maintenance of treatment benefit. The resubmission 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.

7.14 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

AbbVie welcomes the PBAC's recognition that there is a need for subsidised treatment for patients with hidradenitis suppurativa and remains committed to bringing an effective treatment option to market as soon as possible for this high need patient population.
Adalimumab is listed on the ARTG for the continuous treatment of HS in those patients who have demonstrated a response after 12 weeks of therapy.