6.8 USTEKINUMAB
45 mg/0.5 mL injection, 1 x 0.5 mL vial; Stelara®; Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 Authority Required listing for ustekinumab (UST) for treatment of psoriatic arthritis (PsA).

2 Requested listing

2.1 The proposed restriction wording is identical to the currently PBS listings of adalimumab (ADA), etanercept (ETC), golimumab (GOL) and infliximab (INX) for PsA (with the exception of the proposed duration of initial treatment). The full wording of the proposed restrictions is presented in Attachment A of the Commentary (6.8.COM.48).

2.2

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
Initial therapy				
USTEKINUMAB Injections 45mg/0.5ml, 1x0.5ml vial	1	2	Stelara	Janssen Cilag
Continuing therapy				
USTEKINUMAB Injections 45mg/0.5ml, 1x0.5ml vial	1	1	Stelara	Janssen Cilag

Authority required

- Initial 1 (new patients)
- Initial 2 (swapping therapy or re-commencement after a treatment break)
- Continuing treatment for all patients

2.3 The submission proposed a special pricing arrangement for initial therapy with an effective price of [redacted] (DPMQ) to take into account the fact that UST is inferior to ADA at improving joint symptoms. [redacted]

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the clinical evaluation report and TGA Delegate Summary were available.

3.2 This was the first consideration by the PBAC of UST for PsA.

3.3 In November 2009, the PBAC recommended UST for the treatment of chronic plaque psoriasis on the basis of acceptable cost-effectiveness compared with ETC (50 mg/week). The PBAC agreed that the listing of UST on the PBS for chronic plaque psoriasis would offer an alternative therapy with a novel mode of action.

4 Clinical place for the proposed therapy

4.1 The submission's proposed place in therapy for UST would be as an alternative bDMARD for PsA patients who had failed therapy with standard DMARDs. The ESC noted that given the inferior joint response rate claimed by the submission and the drug's different mechanism of action, UST would be unlikely to be used frequently as a first line treatment for PsA. The ESC considered that UST would largely be used as 2nd or 3rd line treatment after failing to respond to treatment with a TNF-α inhibitor.

4.2 The PBAC considered that there are two key components involved in PsA, arthritis and psoriasis. In regard to UST's role in treating the arthritis component of PsA, the PBAC agreed that UST is inferior in joint response rate compared to the TNF-α inhibitors that are currently PBS-listed for the treatment of PsA. In regard to UST's role in treating the psoriasis component of PsA, the PBAC noted that UST has a separate PBS listing for the treatment of psoriasis. The PBAC, therefore, questioned the place in therapy for UST in the treatment of PsA.

5 Comparator

The submission nominated ADA as the main comparator. 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 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of UST and ADA using data from two head-to-head trials comparing UST (PSUMMIT-1 and PSUMMIT-2) to placebo (n=927) and two head-to-head trials comparing ADA (ADA1 and ADA2) to placebo (n=413).

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

Trials and associated reports presented in the submission

Trial	Protocol title/Publication title	Publication citation
Ustekinumab versus placebo		
UST1 (PSUMMIT-1)	NCT01009086 Clinical study synopsis PSUMMIT-1 **24-Week Clinical Study Report PSUMMIT-1** A Phase 3 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Ustekinumab, a fully Human Anti-IL-12/12p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis. **52-Week Clinical Study Report PSUMMIT-1** A Phase 3 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Ustekinumab, a fully Human Anti-IL-12/12p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis. **108-Week Clinical Study Report PSUMMIT-1** A Phase 3 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Ustekinumab, a fully Human Anti-IL-12/12p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis.	 17 Jan 2013 2 May 2013 Not provided with the submission
	Main publication: McInnes I.B., et al 2013. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT-1 trial.	Lancet, 382; 780-789
UST2 (PSUMMIT-2)	NCT01077632 Clinical study synopsis PSUMMIT-2 **24-Week Clinical Study Report PSUMMIT-2** A Phase 3 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Ustekinumab, a fully Human Anti-IL-12/12p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s). **60-Week Clinical Study Report PSUMMIT-2** A Phase 3 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Ustekinumab, a fully Human Anti-IL-12/12p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s).	 17 Jan 2013 4 June 2013
	Ritchlin C., et al 2014. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT-2 trial.	Annals of Rheumatic Disease, 73 (6); 990-999. Includes supplementary data
UST1 and UST2 (Kavanaugh 2014)	Integrated analysis report for PSUMMIT-1 and PSUMMIT-2: Analysis of radiographic data at Week 24 and Week 52 for ustekinumab-treated subjects with active psoriatic arthritis.	13 June 2013
	Main Publication: Kavanaugh A., et al 2014. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials.	Annals of Rheumatic Diseases, 73 (6); 1000-1006. Includes supplementary data.
Adalimumab vs placebo		
ADA1	Mease P, Gladman D D and Ritchlin C et al, Adalimumab for the	Arthritis & Rheumatism

Trial	Protocol title/Publication title	Publication citation
ADEPT M02-518 NCT00646386 Mease 2005	treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomised, placebo controlled trial.	2005; 52(10):3279-3289
	Gladman et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial.	Annals of the Rheumatic Diseases, 2007; 66(2):163-168
	Gladman DD et al. 2007b. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial.	Arthritis & Rheumatism 56(2):476-488.
	Mease P.J., et al 2009. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the adalimumab effectiveness in psoriatic arthritis trial (ADEPT).	Annals of Rheumatic Disease, 68; 702-709.
	Gladman D., et al 2010. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomised controlled trial ADEPT.	Arthritis Research and Therapy, 12; R113.
	Mease P.J., et al 2013. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT.	Journal of Rheumatology, 40(5); 647-652.
ADA2 M02-570 NCT00646178 Genovese 2007	Genovese, M, Mease, P, Thomson, G et al, Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.	Journal of Rheumatology 2007 34(5):1040-1050. [Erratum appears in J Rheumatol. 2007 34(6):1439]

Source: Table B-7, pp47-48 of the submission

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

Key features of the included evidence – indirect comparison

Trial (arms)	N*	Design/ duration	Risk of bias	Patient population	Outcomes
UST versus placebo					
UST1(PSUMMIT-1) - PBO - UST45mg - UST90mg	 206 205 204	R, DB for 24wks, 104 sites (including 14 sites in Australia) EE at wk16[a], cross over for PBO to UST45mg Wks 24-108.	Low	TNF-α naive	ACR20/50/70, PsARC PASI75, HAQ-DI (wk24 &52) some results available at week 12.
UST2(PSUMMIT-2) - PBO - UST45mg - UST90mg	 104 103 105	R, DB for 24 wks, 71 sites in 10 countries, EE at wk16[a], cross over for PBO to UST 45mg Wks 24-60.	Low	TNF-α naïve or experienced	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk24 &52)
ADA versus placebo					
ADA1 (ADEPT) - PBO - ADA 40mg Q2W	 162 151	R, DB for 24 weeks. 16 sites in US and Canada. Crossover for PBO wk24-48, rescue meds after Wk12 with criterion [b]	Low	TNF-α naive	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk12 &24)
ADA2 (M02-570) - PBO - ADA 40mg Q2W	 49 51	R, DB for 12 weeks, 50 sites in 8 countries, crossover for PBO wk12-24	Low	TNF-α naive	ACR20/50/70, PsARC, SF36, HAQ-DI (wk12)

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised, EE=early escape, Q2W=every 2weeks;

Q4W=every 4 weeks, TJC=tender joint count, SJC=swollen joint count, LOCF=last observation carried forward, PASI=Psoriasis Area and Severity Index., HAQ-DI= Health Assessment Questionnaire disability index; ACR 20/50/70=American College of Rheumatology 20%, 50% or 70% improvement criteria, PsARC=Psoriatic arthritis response criteria.

* number of patients analysed.

[a] At Week 16 patients treated with PBO or UST 45 mg with < 5% improvement in TJC and SJC enter early escape with UST 45 mg and UST 90 mg respectively. LOCF was used for efficacy analyses.

[b] rescue meds (corticosteroids or DMARDs) were initiated in patients who failed to have achieved at least a 20% decrease in both SJC and TJC on two consecutive visits, these patients were considered non-responders. Source: Table B.13, p39 of the submission.

6.6 The main difference between the trials is that the ADA trials enrolled anti-TNF-α naïve patients whereas the UST2 (PSUMMIT2) trial recruited both anti-TNF-α naïve and experienced patients. The assessment of treatment response was earlier for the ADA trials (initial response at 12 weeks and continuing response at 24 weeks) and later for UST trials (initial response at 24 weeks and continuing response at 52 weeks). For all trials, placebo treated patients were permitted to cross over to active treatment after the double blind phase, 24 weeks for UST1, UST2 and ADA1; and 12 weeks for ADA2. For the UST trials, for patients in the placebo and UST45mg arms, early escape to either UST45mg or UST90mg respectively was also possible before initial treatment assessment (i.e., at 16 weeks) if patients showed less than 5% improvement in swollen joint count and tender joint count. Last observation carried forward method was used to impute for the efficacy analyses.

Comparative effectiveness

6.7 Response to the currently PBS-listed bDMARDs for PsA is determined by the American College of Rheumatology 20% and 50% improvement criteria (ACR20 and ACR50).

6.8 The submission appropriately nominated ACR50, at 24 weeks for UST and 12 weeks for ADA, as the most relevant outcome for assessing PBS response to treatment for PsA. The submission also appropriately nominated ACR20, ACR70, PASI75, HAQ-DI and PsARC as secondary outcomes. These outcomes measure either the arthritis or the psoriasis component of PsA or the disease related quality of life. The ESC considered that ACR50 was the primary outcome of interest as the more stringent of the two joint responses and given the importance of the joint outcome in the proposed criteria for eligibility for continuing treatment with ustekinumab.

6.9 The submission further presented non comparative data reported at Week 52 for UST and Week 48 for ADA (ADA1) as supportive outcomes to demonstrate continued treatment response.

6.10 The results for ACR50 and ACR20 response for UST (24 weeks) and adalimumab (12 weeks) are presented in the two following figures, respectively.

Results of ACR50 response at Week 24 for UST and Week 12 for ADA across the randomised trials

[This figure has been redacted]

ACR20 response at Week 24 for UST and Week 12 for ADA across the randomised trials

[This figure has been redacted]

6.11 The results of ACR50 and ACR20 at Week 24 for UST and Week 12 for ADA illustrate that whilst both biologics were more effective than placebo at producing a response, fewer patients would attain a response with UST than ADA, even despite an additional 12 weeks of treatment.

6.12 For ACR50 response, for the overall population (anti-TNF-α experienced and naïve patients), statistically significantly fewer patients attained a response with UST versus ADA, with a risk difference (RD) of [redacted] (95%CI: [redacted], [redacted]) UST 45 mg or [redacted] (95%CI: [redacted], [redacted]) for UST 90 mg. This is consistent with results using the relative risk statistic. In the anti-TNF-α naïve population the results of the comparisons were no longer statistically significant (although point estimates of the differences were similar to the overall population, due to small sample sizes), except for UST 45 mg and the pooled UST 45 mg and 90 mg comparison using the RD statistic. There was no significant difference in response between the two UST regimens. The results for ACR20 response generally support the findings of the ACR50 response; all point estimates favoured ADA, reaching statistical significance using the relative risk statistic for the comparisons of UST 45mg and the pooled UST 45mg and 90mg versus ADA in both the overall and TNF-α inhibitor naïve population. Similar results were reported for the outcome of ACR20.

6.13 For the indirect comparisons, the submission reasonably noted some potential sources of heterogeneity:

- The placebo response rate is higher in the UST compared to the ADA trials. For ACR50, the placebo responses were on average [redacted] and [redacted] in the UST and ADA trials respectively. The RD between the two placebo rates is [redacted] (95% CI: [redacted], [redacted]), indicating a statistically significant difference. The submission argued that a higher placebo rate in the UST trials would bias the indirect comparison against UST.
- The submission also noted some differences in the numbers of joints that were included in the ACR assessments of the UST and ADA trials, particularly the inclusion of distal joints in the ADA trials. The submission argued that as these joints are often affected in PsA, their inclusion in ADA trials would bias against UST.

The PBAC acknowledged these issues, but did not consider them adequate to change the overall conclusion of inferiority of UST to ADA in terms of joint response.

6.14 The submission also presented PASI75 response at Week 24 for UST and Week 12 for ADA for patients with ≥3% body surface area with psoriasis. It was considered as a supportive analysis because PASI75 response is not included in the criteria for determining eligibility for PBS-subsidised continuing treatment with UST for PsA. Whilst both UST and ADA were more effective than placebo in terms of PASI75 response, the indirect comparison in general favoured ADA. Although there were no statistically significant differences between UST and ADA, all point estimates favour ADA. The submission considered UST to be of similar efficacy to ADA with respect to inducing in a PASI75 response.

6.15 The submission further provided a comparison of the longer-term maintenance of response to treatment:

- For UST, a post-hoc analysis of the individual patient data from the PSUMMIT trials demonstrated that [redacted] of patients who achieved ACR50 at Week 24 maintained their response to Week 52.
- For ADA, an analysis of persistence to ADA on the PBS (assumed to be representative of maintenance of response) found that of patients receiving treatment at 6 months, [redacted] continued to receive treatment at 12 months. Similar results [redacted] were observed for the 4 to 10 month period, representing the first continuation treatment period of ADA.

6.16 The PBAC agreed with the ESC that this comparison may favour UST. For instance, the [redacted] non-persistence with ADA in the PBS cohort may include reasons other than an inability to maintain response and therefore may underestimate the efficacy of ADA to maintain a response. Moreover, the [redacted] UST response rate from the PSUMMIT clinical trial may overestimate the ability to maintain response to treatment due to the higher compliance that generally occurs during a clinical trial compared with use in standard clinical practice.

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

Comparative harms

6.17 Treatment with UST for up to one year appeared to be generally well tolerated. The incidence of adverse events observed with UST and ADA were similar during the placebo-controlled period, with the majority of adverse events transitory and of mild or moderate severity. The incidence of severe adverse events (meta-analyses: UST 45 mg and 90 mg: [redacted], ADA: [redacted]) and adverse events resulting in treatment discontinuation (meta-analyses: UST 45 mg: [redacted], UST 90 mg: [redacted], ADA [redacted]) were low and similar across the treatment groups.

6.18 The adverse event profile observed with UST and ADA were similar, the most commonly reported adverse events were nasopharyngitis, upper respiratory tract infection and headache, but with a higher incidence observed in patients treated with ADA likely due to the longer duration of reported safety data. Injection site pain ([redacted]) or reaction ([redacted]) was reported in a higher proportion of patients treated with ADA than patients treated with UST (pooled 45 mg: [redacted], pooled 90 mg: [redacted]).

6.19 Through one year of treatment, the incidence of antibodies to UST was low, the incidence of malignancies, cardiovascular events and serious infections were very low with no cases of tuberculosis and no deaths were reported in patients treated with UST.

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

Benefits/harms

6.20 A summary of the comparative benefits for UST versus ADA is presented in the table below.

Indirect comparison - Summary of comparative benefits for ustekinumab and adalimumab

Trial	UST	PBO	ADA	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					UST	PBO	ADA	
Benefits								
ACR50 – all patients: indirect comparison								
UST 45/90mg[a]								
ADA[b]								
Indirect comparison: UST vs ADA								
ACR20 – all patients: indirect comparison								
UST 45/90mg[a]								
ADA[b]								
Indirect comparison: UST vs ADA								

[a] UST = pooled results for UST1 and UST2 trials in TNF-α naïve and experienced patients measured at 24 weeks
[b] ADA = pooled results for ADA1 and ADA2 trials in TNF-α naïve patients measured at 12 weeks
Abbreviations: UST= ustekinumab; ADA = adalimumab; PBO = placebo; RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation

6.21 On the basis of indirect evidence presented by the submission, for every 100 patients treated with UST in comparison to ADA approximately 13 fewer patients would have achieved ACR50 over 24 weeks compared with over 12 weeks.

6.22 An assessment of the comparative harms was not conducted as the adverse events were not reported at comparable time points in the trials.

6.23 The following table presents an additional analysis of an indirect comparison based on ITT for ACR50 response for patients who are anti-TNF-α naïve in the UST trials versus other bDMARDs. This analysis was conducted at the request of the ESC and included in the ESC advice.

Indirect comparison - Summary of comparative benefits for patients who are anti-TNF-α naïve in the UST trials (analysis based on ITT) (the comparison presented in the commentary are of all patients in the UST trials (anti-TNF-α naïve and experienced). The comparisons versus ETN and all bDMARDs were not presented in the submission/commentary.

Trial	Drug	Comparator /PBO	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Drug	Comparator/ PBO	
Benefits						
ACR50 response Week 24 for UST and Week 12-16 for comparators: indirect comparison						

	UST	PBO	ADA	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					UST	PBO	ADA	
Meta-analysis (UST 45&90mg)	[redacted]							
Meta-analysis (ADA)								
Indirect comparison: UST versus ADA								

	UST	PBO	ETN	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					UST	PBO	ETN	
Meta-analysis (UST 45&90mg)	[redacted]							
Meta-analysis (ETN)								
Indirect comparison: UST versus ETN								

	UST	PBO	bDMARD	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					CZP	PBO	bD	
Meta-analysis (UST 45&90mg)	[redacted]							
Meta-analysis (ADA, ETN, GOL, INX)								
Indirect comparison: UST versus (ADA, ETN, GOL, INX)								

Abbreviations: bDMARD= Meta-analysis (ADA, ETN, GOL, INX); bD=bDMARD

6.24 On the basis of indirect evidence presented by the submission, for every 100 anti-TNF-α naïve patients treated with UST in comparison to:

- ADA: approximately 11 fewer patients would have achieved ACR50 over 24 weeks compared with over 12 weeks;
- ETN: approximately 20 fewer patients would have achieved ACR50 over 24 weeks compared with over 12 weeks; and
- All bDMARDs: approximately 15 fewer patients would have achieved ACR50 over 24 weeks compared with over 12-16 weeks.

6.25 An assessment of the comparative harms was not conducted as the adverse events were not reported at comparable time points in the trials.

Clinical claim

6.26 The submission described UST as inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over ADA. The ESC considered that this claim was appropriate.

6.27 With respect to efficacy, the submission also made the following specific claims:

- UST is less effective than ADA at inducing a joint response in the initial treatment period (24 weeks) as assessed by ACR50. The PBAC concurred with the ESC and agreed with this claim.
- UST is as effective as ADA at inducing a skin response in the initial treatment period (24 weeks) as assessed by PASI75. The ESC noted that although none of the differences were statistically significant, the point estimates in the indirect comparison generally favoured ADA over UST. Overall, the PBAC considered that the efficacy of UST in psoriasis is probably non-inferior to adalimumab and other TNF inhibitors.
- The proportion of UST-treated patients with joint and skin responses continues to increase over time (through to 52 and 100 weeks) and achieves a response similar to that of ADA, albeit over a longer period of time. The ESC noted that this claim is based on a comparison of maintenance of response in a clinical trial of ustekinumab and persistence with adalimumab from a sample of PBS data. As detailed above, the PBAC agreed with the ESC that the comparison may favour UST.

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

Economic analysis

6.28 The submission presented a two part economic evaluation based on the results of the indirect comparisons between UST and ADA: 1) a modelled economic analysis for the initiation period to determine a cost for UST that would give a similar cost per responder compared to ADA and 2) a cost minimisation analysis for continuing therapy between UST and ADA.

6.29 A summary of the economic evaluations presented is summarised in the following table.

Summary of economic evaluations

Time frame	Evidence	Main Outcomes	Costs	Method
Initial treatment Ustekinumab: 28 weeks* Adalimumab: 16 weeks	Trial based	ACR 50 PASI 75	Drug acquisition	Calculate the price for ustekinumab at which the cost per responder is the same as adalimumab.
Continuing treatment Ustekinumab: 24 weeks* Adalimumab: 24 weeks	IPD analysis and analysis of PBS utilisation	ACR 50 (UST) PBS persistence data (ADA)	Drug acquisition	Cost minimisation

* meta-analysed data for both 45 mg and 90 mg ustekinumab. ACR American College of Rheumatology score, ADA adalimumab, PASI Psoriasis area and severity index, PBS Pharmaceutical Benefits Scheme, PsARC Psoriatic arthritis response criteria UST ustekinumab; IPD=individual patient data.

Source: Table D.1, p130 of the submission.

6.30 The steps involved to calculate initial treatment cost effectiveness analysis presented in the submissions' estimation of a price for UST are described below:

- Calculate the incremental cost per additional responder over placebo (i.e. ICERs) for each outcome for ADA.
- Using the risk difference associated with UST versus placebo for each outcome, calculate the price of UST for the initial treatment period at which the incremental cost per additional responder over placebo is equal to that of ADA for each

outcome.

- Finally, a weighted price based upon both skin involvement and joint involvement is calculated.

6.31 The results of Part 1 and Part 2 of the economic evaluation are presented in the following table and the table on page 15, respectively.

Cost per additional responder for adalimumab by outcome

Outcome	Incremental RD (response to initial ADA versus placebo)	Cost of ADA for initial therapy (providing 16 weeks of therapy)	Cost per additional responder for ADA	Incremental RD[a]	Cost of UST for initial therapy to achieve equal cost effectiveness	Cost per dose of UST to achieve equal cost per additional responder (DPMQ)
	A	B	C = B /A	D	E= DxC	F=E/3 doses
ACR 20	[redacted]	DPMQ for ADA is [redacted] for 2 doses, four packs are required for initiation therapy Total cost for initiation is: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR 50*	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
ACR 70	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PASI 75*	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PsARC	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Estimated DPMQ of UST using 50:50 weight of ACR50 and PASI75 outcomes						[redacted]
Estimated DPMQ of UST using [redacted] weight of ACR50 outcome						[redacted]

Abbreviations: ACR American College of Rheumatology score, ADA adalimumab, PASI Psoriasis area and severity index, PsARC Psoriatic arthritis response criteria [a] (response to initial UST versus placebo) Source: Tables D.5 and D.6, p136 of the submission. Sheet 'Cost effectiveness Initial", Section_D_Ustekinumab_v_Adalimumab.xls

6.32 Although a cost per additional responder is summarised for each outcome, the weighted price of UST for initiation therapy over 28 weeks was determined by assuming a [redacted] weight of ACR50 and PASI75 outcomes. The PBAC considered the [redacted] weight assumption was not an appropriate basis to determine the price of UST on the PBS. Although psoriasis outcomes may be an important component of PsA, psoriasis outcomes or PASI75 are not relied on by the PBS to determine response to treatments for PsA. As per the submission's own arguments, the most important outcome for determining PBS response is ACR50, thus this should be the only outcome to be relied on for determining a DPMQ for UST.

6.33 The PSCR acknowledged (p3) that the continuing criteria are based on achieving an ACR50. However, the response argued that as PsA is a disease of the joints, tendons and skin, basing the price for UST on achieving ACR50 alone would implicitly reduce the value of any skin improvements associated with UST. The ESC considered that given the importance of the joint outcome in the eligibility criteria for continuing treatment with UST, a conservative approach would set the price based only on the ACR50 outcome. The PBAC agreed with the ESC that it would be more appropriate for the calculation of the price to be based on the ACR50 outcome alone.

6.34 The evaluation noted that the submission's analysis also did not take into account potential QALY decrements associated with UST therapy. Since longer treatment would be required with UST to attain a response, even with an additional 12 weeks of therapy, fewer patients treated with UST attain a response than those treated with ADA over 12 weeks. Accordingly, the price at which UST is cost-effective versus ADA has been overestimated.

6.35 The PSCR calculated the time difference in the ACR50 health state for patients who received UST to be [redacted] less compared with ADA treated patients. The ESC considered that this estimate ignores the fact that after 12 weeks, ADA non-responders could switch to an alternate bDMARD, whereas patients treated with UST must persist with it for another 12 weeks to determine response. All currently PBS listed bDMARDs are more effective than UST with respect to ACR50 response (as illustrated in the table of ACR50 response at Week 24 for UST and Week 12 for ADA across the randomised trials).

Cost minimisation analysis of UST versus ADA for continuing therapy

	Adalimumab	Ustekinumab
Continuing Treatment Calculations		
Number of doses	12	[redacted]
Cost of drug per dose (Dispensed price per dose)	$887.29	[redacted]
Total Cost	[redacted]	
Cost calculations at current list price		
Dispensed price per dose	$887.29	[redacted]
Total Cost	$10,647.42	[redacted]
Savings accrued over 6 months with current price	NA	[redacted]
Savings expressed as % with current price	NA	[redacted]

Source: Table D.7, p138 of the submission and Section D Excel workbook accompanying the submission.

6.36 The submission did not clearly state the dose relativity between ADA and UST for continuing therapy. Based on the data presented, it was assumed that the submission was claiming a dose relativity of: UST45mg or 90mg every 12 weeks; ADA 40mg every 2 weeks.

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

Drug cost/patient/course

6.37 [redacted] over 28 weeks for initial therapy and [redacted] over 24 weeks for continuation therapy.

Estimated PBS usage & financial implications

6.38 This submission was not considered by DUSC.

6.39 Appropriately, a market share approach was used to estimate the financial impact of UST listing.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
E.2: Estimated use of UST and cost to PBS/RPBS					
Sc TNF-α scripts for PsA					
Patients who will uptake UST					
New initiations					
Switching therapies					
UST scripts					
Initial					
Continuing					
UST cost to PBS/RPBS[a]					
Initial					
Continuing					
E.3: Estimated change in ADA as proxy for all other PBS listed SC TNF-α inhibitors and cost to PBS/RPBS assuming UST initial therapy will replace 28 weeks of ADA and UST continuing therapy will replace 24 weeks of ADA					
ADA scripts(2 doses per script)					
28 weeks of ADA replaced					
24 weeks of ADA replaced					
ADA cost to PBS/RPBS[a]					
28 weeks of ADA replaced					
24 weeks of ADA replaced					
E.4: Estimated net cost to the PBS/RPBS					
Net cost to PBS/RPBS[a]					
28 weeks of ADA replaced					
24 weeks of ADA replaced					

[a] Net of patient co-payments, SC=subcutaneous injection

Source: pp146-155 of the submission.

6.40 The numbers of scripts may be inaccurate due to: 1) the estimated size of the bDMARD market, a relatively flat increase was assumed in the submission; 2) the assumed uptake rates for UST (based on sponsor's prior experience with infliximab and golimumab for PsA); 3) the numbers of patients likely to be switching to UST, the dataset used by the submission did not include patients who are re-entering treatment with biologicals after a prolonged break.

6.41 The submission's estimate of the cost of listing of UST for PsA may not be entirely reasonable due to: 1) inappropriate estimation of the cost offsets associated with substituted therapies with ADA. It was inappropriate to assume that an initial course of UST would displace 28 weeks of therapy with ADA, this is because the assessment of ADA treatment efficacy occurs at week 12, and those who do not respond will not continue treatment. Although the patients may switch to an alternate bDMARD, this is unlikely to happen immediately and some patients would have reached their maximum number of treatments in a biologic cycle and would have to discontinue treatment for 5 years; 2) the omission of potential additional cost for help with injections. The lack an auto-injector presentation for UST may result in greater services being required for UST administration versus ADA or ETC where an auto injector pen is available. However fewer injections are required with UST.

6.42 The submission predicted a net saving of UST to the government over 5 years of less than $10 million. This is driven mostly by the assumed cost savings of replacing 28 weeks of treatment with ADA. As discussed above, this is based on an

unreasonable assumption; the actual saving to PBS would be likely much less than predicted.

Quality Use of Medicines

6.43 Quality use of medicine initiatives were proposed for UST with the main goal of educating and supporting healthcare professionals and consumers to ensure appropriate use.

Financial Management – Risk Sharing Arrangements

[redacted]

7 PBAC Outcome

7.1 The PBAC rejected a request to list UST as an Authority Required benefit for the treatment of PsA on the basis of evidence of inferior effectiveness to ADA, particularly in terms of joint response, and a lack of compelling evidence of clinical need despite its different mechanism of action to the anti-TNF-α agents currently PBS listed for the treatment of PsA.

7.2 The PBAC considered that there are two key components involved in PsA, arthritis and psoriasis. In regards to UST's role in treating the arthritis component of PsA, the PBAC agreed that UST is inferior in joint response rate compared with the TNF-α inhibitors that are currently PBS-listed for the treatment of PsA. In regards to UST's role in treating the psoriasis component of PsA, the PBAC noted that UST has a separate PBS listing for the treatment of psoriasis. The PBAC, therefore, questioned the place in therapy for UST in the treatment of PsA.

7.3 The PBAC considered that ADA was appropriately nominated as the appropriate main comparator. The PBAC also considered that ETC and GOL would be appropriate secondary comparators.

7.4 The PBAC noted the submission presented an indirect comparison of UST and ADA using data from two head-to-head trials comparing UST (PSUMMIT-1 and PSUMMIT-2) to placebo (n=927) and two head-to-head trials comparing ADA (ADA1 and ADA2) to placebo (n=413). The submission nominated ACR50, at 24 weeks for UST and 12 weeks for ADA, as the primary outcome; and ACR20, ACR70, PASI75, HAQ-DI and PsARC as secondary outcomes.

7.5 Since the outcome used to determine eligibility for continuing treatment in the current PBS listed restriction for PsA is a combination of ACR50 and ACR20, the PBAC agreed with the ESC that ACR50 was the outcome of most interest. ACR50 is more stringent than ACR20 and reflects to a greater degree the criteria for the current PBS eligibility for continuing treatment with a bDMARD.

7.6 Based on the data presented, the PBAC noted that all point estimates for ACR50 and ACR20 favoured ADA, reaching statistical significance based on the relative risk statistic for the comparisons of UST 45mg and the pooled UST 45mg and 90mg versus ADA in both the overall (anti-TNF- α experienced and naïve patients) and TNF-α inhibitor naïve populations. The PBAC also noted that the time taken to achieve maximum ACR50 and ACR20 responses were longer with UST compared to ADA. The PBAC also noted that the placebo rate for ACR50 outcome, on average, is higher in the UST trials compared to the ADA trials ([redacted] v.s. [redacted]). Although the PBAC considered that there is no obvious explanation for the different placebo response rates between the UST and ADA trials, this finding did not influence the Committee's overall conclusion of inferiority.

7.7 The PBAC noted the submission presented PASI75 response at Week 24 for UST and Week 12 for ADA for patients with ≥3% body surface area with psoriasis as a supportive analysis. The PBAC noted that whilst both UST and ADA were more effective than placebo in terms of PASI75 response, and all point estimates also favoured ADA, there were no statistically significant differences between UST and ADA. The PBAC considered that UST in psoriasis is, on balance, probably non-inferior to ADA and other TNF inhibitors in terms of effectiveness.

7.8 Based on the indirect comparison, of comparative benefits (ACR50) for patients who are TNF-α inhibitor naïve in the UST trials (ITT) versus ENT and all bDMARDs (conducted by the evaluators; see section 6.23), the PBAC considered that UST in PsA is also inferior to ENT and other TNF inhibitors in terms of effectiveness.

7.9 The PBAC noted the incidence of adverse events observed with UST and ADA was similar during the placebo-controlled period, with the majority of adverse events transitory and of mild or moderate severity. The adverse event profiles observed with UST and ADA were also similar, the most commonly reported adverse events were nasopharyngitis, upper respiratory tract infection and headache, but with a higher incidence observed in patients treated with ADA likely due to the longer duration of reported safety data.

7.10 The PBAC agreed with the submission's claim that UST is inferior to ADA in terms of comparative effectiveness and equivalent in term of comparative safety. However, the PBAC did not accept the submission's claim that the proportion of UST-treated patients with joint and skin responses increases over time (through to 52 and 100 weeks) and achieves a response similar to that of ADA, albeit over a longer period of time. The PBAC agreed with the ESC that this claim was based on an asymmetrical comparison of maintenance of response in a clinical trial of UST and persistence with ADA from a sample of PBS data.

7.11 The PBAC noted that the submission presented the economic evaluation in two parts, a form of cost effectiveness analysis for the initiation phase and a cost minimisation for the continuing phase The PBAC considered this approach was not appropriate and recalled that it has not previously accepted different prices for initiation and continuing therapy with any of the bDMARDs that it has recommended for PBS listing for PsA.

7.12 The PBAC further noted that the submission applied a [redacted] weighted price based upon both skin involvement (PASI75 outcome) and joint involvement (ACR50 outcome) in the cost effectiveness analysis for the initiation phase.

7.13 The PBAC noted the PSCR argued that as PsA is a disease of the joints, tendons and skin, therefore to base the price of UST on achieving ACR50 alone would implicitly reduce the value of any skin improvements associated with UST. The PBAC recalled that the utility gain of an improvement in psoriasis has not been previously considered in PsA applications. Furthermore, the PBAC noted that an article by Cohen, Reda and Clegg (The Journal of Rheumatology 1999, 26(8):1752-1756) described the relationship between psoriasis and PsA is weak and that many patients with severe PsA do not have severe psoriasis. Hence, the PBAC considered that the sponsor's argument is not valid; and that an appropriate basis to determine the price of UST is on ACR50 outcome alone.

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

Janssen submitted ustekinumab for the treatment of psoriatic arthritis following requests for a bDMARD with an alternate mechanism of action for these patients.
Although disappointed by the PBAC's decision, Janssen remains committed to working with the PBAC to enable patient access to ustekinumab for those in need.