

6.3 CERTOLIZUMAB PEGOL 200 mg/mL injection, 2 x 1 mL syringes; Cimzia®; UCB Australia Pty Ltd.

1 Purpose of Application

- 1.1 Authority Required listing for certolizumab (CZP) for treatment of psoriatic arthritis (PsA).

2 Requested listing

- 2.1 The proposed restriction wording is identical to the currently PBS listing of adalimumab (ADA), etanercept (ETC), golimumab (GOL) and infliximab (INX) for PsA. The full requested restriction is presented in Attachment A.2 of the Commentary (6.3 COM.42).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
Initial and continuing treatment CERTOLIZUMAB PEGOL Injection, 200mg/ml, 2x1ml syringes	1	5	Cimzia	UCB
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 requested listing of CZP was made on a cost minimisation basis versus ADA (main comparator).

3 Background

- 3.1 CZP was TGA approved on 1 May 2014 for the treatment of adult patients with active PsA where response to previous disease modifying anti-rheumatic drugs (DMARDs) is inadequate.
- 3.2 This was the first consideration of CZP by the PBAC for PsA. CZP is currently listed on the PBS for treatment of severe active rheumatoid arthritis (RA) (recommended March 2010) and for treatment of active ankylosing spondylitis (AS) in patients who meet certain criteria (recommended March 2014). Both listings were on a cost minimisation basis versus ADA.

4 Clinical place for the proposed therapy

- 4.1 The submission’s proposed place in therapy for CZP was as an alternative bDMARD for PsA patients who have failed therapy with standard DMARDs.

5 Comparator

- 5.1 ADA was nominated as the primary comparator for cost minimisation analysis. ETC, GOL and INX were nominated as important secondary comparators. The nominated comparators were considered appropriate.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

- 5.2 The ESC noted that ustekinumab (UST) was not nominated as a comparator in the submission but that the UST trial results were used in Bayesian MTC analysis. The ESC considered this was not appropriate as UST is not currently PBS listed for this indication and has a different mechanism of action.

The PBAC noted that the MTC results for the outcome of most interest, the ACR50 at 12-16 weeks, do not include UST.

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 through the online portal. There were 3 supporting letters received from rheumatologists.

Clinical trials

- 6.3 The submission was based on placebo controlled trials of CZP (n=1), ADA (n=2), ETC (n=2), GOL (n=1), INX (n=2) and UST (n=2).
- 6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial IDs	Protocol title/Publication title	Publication citation
Current PBS comparators		
Certolizumab vs placebo		
RAPID-PsA PSA001 NCT01087788	Additional new indication in Psoriatic Arthritis based on Phase III clinical Trial (PsA001). Cimzia® Certolizumab Pegol Module 5, interim clinical study reports PSA001. (UCB Biosciences GmbH).	October 2012
	Mease. P, Fleischmann, R, et al. 2014, Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week	Ann Rheum Dis, 2014, 73:48-55.

Public Summary Document – November 2014 PBAC Meeting

Trial IDs	Protocol title/Publication title	Publication citation
Current PBS comparators		
	results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA).	
	Van der Heijde, Fleischmann, et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol.	Ann Rheum Dis, 2013, published online
Adalimumab vs placebo		
ADA1 ADEPT M02-518 NCT00646386	Mease P, Gladman D D and Ritchlin C et al, Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomised, placebo controlled trial.	Arthritis & Rheumatism 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
ADA2 M02-570 NCT00646178	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]
Etanercept vs placebo		
ETC1 20021630 Mease (2004) NCT00317499	Mease, Kivitz, et al, Etanercept treatment of psoriatic arthritis; safety, efficacy, and effect on disease progression.	Arthritis and Rheumatism 2004; 50(7):2264–2272
	Mease, Woolley and Bitman, et al. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction.	J Rheumatol, 2011; 38(11):2461-5.
	Mease, Woolley and Singh, et al, Patient-reported outcomes in a randomised trial of etanercept in psoriatic arthritis.	Journal of Rheumatology, 2010; 37(6):1221-7.
ETC2 Univ. of Washington Mease (2000)	Mease, Goffe, et al, Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.	Lancet 2000; 356:385–390
Golimumab vs placebo		
GOL1 GO-REVEAL NCT00265096	Kavanaugh, McInnes, et al, Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis.	Arthritis & Rheumatism 2009; 60(4):976–986.
	Kavanaugh, van der Heijde, et al. 2012) Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomised, placebo-controlled trial.	Arthritis Rheum, 2012; 64(8):2504-17.
Infliximab vs placebo		
INX1 IMPACT	Antoni, et al, Sustained Benefits of Infliximab Therapy for Dermatologic and Articular Manifestations of Psoriatic Arthritis: Results From the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT).	Arthritis and Rheumatism, 2005; 52(4):1227–1236
	Kavanaugh, A, Antoni C.E., et al, The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year.	Annals of the Rheumatic Diseases; 2006; 65(8):1038-43.
INX2 IMPACT2 NCT00051623	Antoni, et al, Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150–1157	Ann Rheum Dis, 2005;64:1150–1157
	Van der Heijde, Kavanaugh, et al, Infliximab inhibits progression of	Arthritis & Rheumatism,

Trial IDs	Protocol title/Publication title	Publication citation
Current PBS comparators		
	radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2.	2007; 56(8):2698-707.
	Kavanaugh A., Antoni C, and Krueger G.G, et al, Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis.	Annals of the Rheumatic Diseases, 2006; 65(4):471-7.
Potential future PBS comparator		
Ustekinumab versus placebo		
UST1 (PSUMMIT-1)	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)	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.

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

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

Key features of the included evidence – indirect comparison

Trial (arms)	N*	Design/ duration	Risk of bias	Patient population	Outcomes	PBAC seen before?
Certolizumab 200mg q2w and 400mg q2w versus placebo						
CZP1 Rapid PsA (Mease 2014)	409	R, DB wks0-24, EE ^a for PBO at 16wks, crossover for PBO at 24wks. Dose blind Wk24-48 following re-randomisation of PBO to CZP, OL Wk48-216.	Uncertain [^]	TNF α naive or experienced	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk12 &24)	No
Current PBS comparators						
ADA 40mg SC q2w versus placebo						
ADA1 (ADEPT)	313	R, DB for 24 weeks. Crossover for PBO wk24-48, rescue meds after Wk12 with criterion ^p	Low	TNF- α naive	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk12 &24)	Yes
ADA2 (M02-570)	49 51	R, DB for 12 weeks, crossover for PBO wk12-24	Low	TNF- α naive	ACR20/50/70, PsARC, SF36, HAQ-DI (wk12)	Yes
ETC 25mg SC twice weekly versus placebo						
ETC1 (Mease 2004)	205	R, DB for 24wks, OL and crossover for PBO wk24-72.	Low	TNF- α naive	ACR20/50/70, PsARC, HAQ-DI (wk12 &24) PASI50/75/90, SF36 (wk 24)	Yes
ETC2 (Mease 2000)	60	R, DB for 12 weeks	Low	TNF- α naive	ACR20/50/70, PsARC PASI50/75, HAQ-DI (wk12)	Yes
GOL 50mg SC q4w and 100mg q4w versus placebo (only 50mg q4w is TGA approved for PsA)						

GOL1 (Go-Reveal)	405	R, DB for 24 wks, EE at wk16 ^a , crossover for PBO at Wk24	Low	TNF- α naive	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk14 &24)	Yes
INX 5mg/kg IV at Weeks 0, 2, 5 and Q8w thereafter versus placebo						
INX1 (IMPACT)	104	R, DB for 16wks, crossover for PBO at wk16 to Wk50.	Low	TNF- α naive	ACR20/50/70, PsARC PASI50/75/90*, HAQ-DI (wk16)	Yes
INX2 (IMPACT2)	200	R, DB for 24 wks, EE for PBO patients at Wk16 ^a	Low	TNF- α naive	ACR20/50/70, PsARC PASI50/75/90, SF36, HAQ-DI (wk14 &24)	Yes
Potential future PBS comparator (ustekinumab)						
UST 45mg and 90mg SC at 0, 4, and Q12W thereafter versus placebo						
UST1 (PSUMMIT-1)	615	R, DB for 24wks, EE at wk16 ^c , 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.	No
UST2 (PSUMMIT-2)	312	R, DB for 24 wks, EE at wk16 ^c , 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)	No

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised, EE=early escape, Q2W=every 2 weeks; Q4W=every 4 weeks, TJC=tender joint count, SJC=swollen joint count, LOCF=last observation carried forward, PASI=

* number of patients analysed.

[^] In Rapid-PsA, there was potential for trial personnel to become unblinded to patient treatment assignments. This is because the prefilled syringes containing either CZP or placebo (saline) have slightly different viscosities and colours (CZP slightly yellow, saline is clear). However the trial report stated that to maintain blinding pharmacokinetic data and antibody data were provided only after the study was unblinded for the first interim analysis.

* PASI results of INX1 (IMPACT trial) were not included in the indirect comparisons as it had a different definition.

^a patients who did not achieve 10% decrease in TJC and SJC switched to either active treatment (if on PBO) or higher dose randomised treatment (if already receiving active treatment eg. GOL50mg moved to GOL100mg). For efficacy analysis patients who met early escape either had their results (at time of EE) carried forward (GOL1) or were counted as non-responders

^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.

^c 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.

Source: compiled during the evaluation, pp49-56 of the submission.

Comparative effectiveness

- 6.6 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). In the trials, ACR response was assessed at Weeks 12-16 and Week 24 (in some trials).
- 6.7 The submission nominated ACR20 at 12 weeks as the primary outcome and ACR20 and ACR50 at 12-16 weeks and 24 weeks and PASI75 at 24 weeks as the secondary outcomes.
- 6.8 Since the outcome used to determine eligibility for continuing treatment, as noted in the proposed restriction, is a combination of ACR50 and ACR20, the ESC considered that ACR50 should be considered as the primary outcome of interest. ACR50 is more stringent than ACR20 and reflects to a greater degree the criteria for eligibility for

continuing treatment with a biological disease modifying anti-rheumatic drug (bDMARD).

- 6.9 To investigate the effect of covariates on the indirect comparisons, the submission commissioned a set of analyses using two-stage regressions. First a meta-regression for a given covariate (e.g., placebo rate) was conducted using data from all TNF- α inhibitors (i.e. excluding UST from Step 1). This meta-regression assumed that all treatments within the class share a common effect. Second, the estimate of the mean (beta (b) and its dispersion (80% credible interval (CrI))) was used to generate a prior for the covariate in a new MTC, one which did not assume that all treatments in anti-TNF share a common effect and UST was added back in Step 2.
- 6.10 The submission justified using a Bayesian MTC to investigate and adjust for the heterogeneity between the trials. The submission argued that due to improvements in standard of care, the absolute efficacy of placebo treatments increases with time, but the absolute efficacy of biologics remained within a steady range. This change would bias against CZP as the RAPID-PsA trial was one of the most recent trials conducted. The ESC considered that the Bayesian MTC is an appropriate methodology for adjusting for both between-trial heterogeneity and uncertainty in between-trial heterogeneity across the multiple trials being compared, relative to either frequentist random-effects or fixed effects (frequentist or Bayesian) model alternatives. However, ESC was concerned that using a Bayesian MTC it becomes difficult to separate genuine non-inferiority from the wide, non-significant intervals associated with large levels of heterogeneity between multiple trials. Replicating these results using a smaller number of more comparable studies would be more convincing and constitute a useful and advisable sensitivity analysis.
- 6.11 Results of the adjusted indirect comparisons of CZP and its comparators using Bayesian meta-regressions for the outcomes of interest (ACR20 and ACR50 response at Weeks 12-16 and Week 24) are summarised in the table below. Due to population heterogeneity, the indirect comparisons were conducted for the TNF- α inhibitor naïve population. As a comparison, results of the unadjusted indirect comparison using methods reported by Bucher et al (1997) are also presented.

Crude event rates are summarised in the following Figures:

ACR20 response at Weeks 12-16

[FIGURE REDACTED]

ACR50 response at Weeks 12-16[^]

[FIGURE REDACTED]

- 6.12 Results of ACR20 and ACR50 at Weeks 12-16 illustrate that whilst all biologics were more effective than placebo at producing a response, the magnitude of the benefit varied. There were no significant differences between the two CZP regimens with respect to efficacy, so their results were pooled in the indirect comparison versus the comparators. Using standard indirect comparison methodology, in the anti-TNF- α naïve population, the results for ACR50 were generally consistent with those of

ACR20 and indicated inferiority of CZP versus existing PBS listed bDMARDs. Similarly, the indirect RD results indicated a similar direction of effect to the RR estimates, but some comparisons were no longer statistically significant (i.e. versus ADA and GOL).

- 6.13 The results from the two CZP dosing regimens did not significantly differ from each other thus their results were pooled in the meta-analysis.

Results of ACR20 and ACR 50 response at Week 12-16 and Week 24 across treatments (Anti-TNF naïve population) (random effects model for adjusted MTC and unadjusted relative risks estimated using frequentist statistics and indirect comparisons following methods reported by Bucher et al (1997).

Intervention	ACR20				ACR50			
	12-16 weeks		24 weeks		12-16 weeks		24 weeks	
RR [95% CI], bDMARDs vs. Placebo								
	Unadjusted frequentist	Adjusted MTC	Unadjusted frequentist	Adjusted MTC	Unadjusted frequentist	Adjusted MTC	Unadjusted frequentist	Adjusted MTC
b (mean) CrI	-	-1.19	-	-0.75	-	-1.02	-	-0.85
CZP Pooled	2.10 [1.50, 2.93]	3.73	2.29 [1.64, 3.18]	2.91	2.65 [1.57, 4.48]	8.91	2.86 [1.77, 4.61]	5.13
ADA	3.51 [2.27, 5.41]	3.22	3.79 [2.56, 5.63]	2.98	9.96 [4.69, 21.17]	8.19	6.25 [3.32, 11.76]	5.24
ETN	4.15 [2.71, 6.36]	4.01	3.68 [2.17, 6.22]	2.77	13.51 [5.03, 36.28]	10.69	9.52 [3.52, 25.75]	5.19
GOL	5.73 [3.10, 10.57]	3.02	4.20 [2.51, 7.03]	2.82	17.03 [4.22, 68.75]	7.62	9.09 [3.38, 24.50]	4.56
INX	5.71 [3.53, 9.25]	3.73	3.38 [2.08, 5.48]	2.82	14.73 [5.11, 42.43]	9.43	10.25 [3.81, 27.55]	5.68
UST45mg	1.92 [1.42, 2.61]	2.82	1.86 [1.38, 2.50]	2.2	NR	NR	2.78* [1.81, 4.27]	3.07
RR [95% CI], CZP Pooled vs. bDMARDs								
ADA	0.60 [0.35, 1.04]	1.16	0.60 [0.36, 1.01]	0.98	0.27 [0.11, 0.67]	1.09	0.45 [0.21, 1.01]	0.98
ETN	0.51 [0.30, 0.87]	0.93	0.62 [0.33, 1.16]	1.05	0.20 [0.06, 0.60]	0.84	0.30 [0.1, 0.91]	0.99
GOL	0.37 [0.18, 0.74]	1.22	0.55 [0.30, 1.01]	1.03	0.15 [0.04, 0.70]	1.17	0.32 [0.11, 0.95]	1.12
INX	0.37 [0.21, 0.66]	1	0.68 [0.38, 1.22]	1.04	0.18 [0.06, 0.59]	0.94	0.28 [0.09, 0.84]	0.9
UST45mg	1.08 [0.70, 1.67]	1.31	1.23 [0.81, 1.88]	1.32	NR	NR	1.21* [0.64, 2.27]	1.66
Dres	-	106.6	-	88.21	-	79.96	-	80.88
pD	-	17.86	-	14.29	-	14.31	-	13.96
DIC	-	124.5	-	102.5	-	94.27	-	94.84

Bolded typography indicates statistically significant results. Abbreviation: b Abbreviations: Dres (residual deviance), effective number of parameters, DIC=smaller numbers indicate better model fit. b=beta estimate for placebo rate from the MTC, if beta=-1, the effect of placebo rate in any given study is completely removed, so the analysis is basically comparing absolute effects. CrI=credible interval

* includes both TNF- α inhibitor naïve and experienced patients.

Source: Tables B-47 (p111) and B-49 (p114) (UCB Biosciences GmbH 2014), Table 9, p.11, Appendix C, Relative Risk Results-Placebo Effect.xlsx, ACR20_12wks_Placebo_Random, ACR20_24wks_Placebo_Random

- 6.14 The ESC noted that the results of the adjusted MTC contradicted the conclusions derived from standard indirect comparisons. Standard unadjusted indirect comparisons suggested CZP to be inferior to all currently PBS listed bDMARDs in terms of ACR20 and ACR50 response. All point estimates of differences in treatment effect did not favour CZP and were statistically significantly worse than currently PBS

listed bDMARDs for ACR20 and ACR50 outcomes at Weeks 12-16 (except for ADA for ACR20) using the standard indirect relative risk statistic.

- 6.15 By contrast, the adjusted MTC did not find any statistically significant differences between CZP and other comparators for either ACR20 or ACR50 response at any time point. Based on the MTC results, particularly the results for ACR20 at Week 12-16, the submission claimed that since the lower 95% CI of CZP versus ADA is 0.60 (thus exceeding the nominated MCID of 0.46) non-inferiority of CZP to ADA can be established.

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

Comparative harms

- 6.16 Comparative safety data were not provided in the submission due to a lack of available or consistent presentation of safety information. However, the absolute risk of adverse events did not appear to differ significantly across the bDMARDs treatment. Overall, additional evidence available beyond the randomised controlled trials supported the safety profile were provided. Comparatively, the safety profile of CZP was considered to be consistent with that expected of a bDMARD used in rheumatological indications.

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

Benefits/harms

- 6.17 No statistically significant differences in the proportion of patients achieving ACR50 response at 12 weeks were observed between CZP and ADA or ETC in the MTC presented in the submission.
- 6.18 There are no statistically significant differences in the safety profiles of CZP, ADA or ETC.

Clinical claim

- 6.19 The submission described CZP as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over ADA, ETC, GOL and INX.

For PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.20 The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as CZP 400mg at 0, 2, 4 followed by 200mg q2w or 400mg q4w versus ADA 40mg q2w. These were based on doses that were used in the trials.
- 6.21 As was the case for the RA and AS indications, treatment with CZP compared to ADA has higher costs upfront due to the need for loading doses. For the RA and AS indications, the DPMQ of CZP was estimated using cost analysis of CZP versus ADA over a typical 2 year treatment period. The results of the analysis using the effective price is summarised in the table below. It was estimated that treatment with CZP over

a 2 year period (based on the effective price) results in an overall cost saving to government with an undiscounted saving of \$ [REDACTED]. This was mainly driven by cost savings derived during continuing therapy. A similar analysis using the published price resulted in an additional cost of \$ [REDACTED] for CZP over 2 years.

Cost of treatment over 2 years - CZP versus ADA at the effective price

		CZP 200	CZP 400	CZP combined	ADA	Difference*	
Unit cost (DPMQ) (delivers one dose)		[REDACTED]	[REDACTED]	-	[REDACTED]	-	
Weight		[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]	
Year 1 (52 weeks)	Initial	Scripts	[REDACTED]	[REDACTED]	-	[REDACTED]	
		Weeks	[REDACTED] ^c	[REDACTED] ^c	-	[REDACTED] ^c	
		Cost	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Continuing	Scripts	[REDACTED]	[REDACTED]	-	[REDACTED]	
		Weeks	[REDACTED] ^d	[REDACTED] ^d	-	[REDACTED] ^d	
		Cost	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Initial + continuing weeks		[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]
	Wastage		[REDACTED] ^a	[REDACTED]	-	[REDACTED]	[REDACTED]
	Year 1 cost		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Year 2 (52 weeks)	Scripts		[REDACTED]	[REDACTED]	-	[REDACTED]	
	Weeks		[REDACTED]	[REDACTED]	-	[REDACTED]	
	Wastage		[REDACTED]	[REDACTED]	-	[REDACTED]	
	Annual cost (non-disc.)		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
	Year 2 cost (disc. [REDACTED]%)		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
Total cost over 2 years (non-discounted)		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
Total cost over 2 years (disc. [REDACTED]%)		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	

Abbreviations: CZP=certolizumab; ADA=adalimumab

* CZP combined minus ADA

^a wastage due to additional continuing script required for 52 weeks with the 200mg regimen compared to 400mg regimen, due to 2 fewer weeks of initial treatment.

^c this is the time the next dose is due.

^d 52 weeks minus initial treatment period.

Source: Table D-4, p156 of the submission Section D worksheet excel spreadsheet.

6.22 Given the proposed PBS listing of CZP was segregated into initial and continuing therapy, a cost comparison of the effective price of CZP versus ADA for these separate phases was also required to establish cost minimisation. This was conducted during the evaluation and is summarised in the table below.

Comparison of the PSB cost of CZP and ADA for initial and continuing treatment of PsA

		CZP 200	CZP 400	ADA	Difference
Initial	Scripts	6 scripts	6 scripts	4 scripts	-
	Weeks	18 weeks	20 weeks	16 weeks	
	Cost	[REDACTED]	[REDACTED]	[REDACTED]	
Continuing	Scripts	6 scripts	6 scripts	6 scripts	-
	Weeks	24 weeks	24 weeks	24 weeks	
	Cost	[REDACTED]	[REDACTED]	[REDACTED]	
Total after one round	Cost	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: constructed during the evaluation

- 6.23 At the effective price, a course of initial treatment with CZP compared with ADA would have a net cost to government of \$ [REDACTED], whereas a course of continuing treatment would have a net savings of \$ [REDACTED]. After one round of initial and continuing therapy, treatment with CZP would result in a cost saving of \$ [REDACTED].

Drug cost/patient/course

- 6.24 As shown in the table above, \$ [REDACTED] (for initiation therapy up to 20 weeks, 6 scripts) and \$ [REDACTED] every 24 weeks (6 scripts) for continuing therapy in responders. Compared to ADA: \$ [REDACTED] for initiation providing up to 16 weeks (4 scripts) treatment and \$ [REDACTED] every 24 weeks (6 scripts) for continuing therapy in responders. In responders, CZP would result in a cost saving to government, after 2 years of continued treatment CZP costs \$ [REDACTED] versus \$ [REDACTED] for ADA. However in non-responders, cost of treatment with CZP would be greater than ADA (\$ [REDACTED] extra) due to higher costs associated with the loading doses.

Estimated PBS usage & financial implications

- 6.25 This submission was not considered by DUSC.
- 6.26 A market share approach was used to estimate the financial impact of CZP listing on PBS for PsA. This was considered appropriate.
- 6.27 The estimated use and financial implications of listing CZP on the PBS for PsA is summarised in the table below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
E.2: Estimated use of CZP and cost to PBS/RPBS					
bDMARD scripts for PsA					
CZP scripts					
Initial					
Continuing					
CZP cost to PBS/RPBS ^a					
Initial					
Continuing					
E.3: Estimated change in ADA, ETC, GOL and cost to PBS/RPBS					
ADA,ETC,GOL scripts					
Initial					
Continuing					
ADA,ETC,GOL cost to PBS/RPBS ^a					
Initial					
Continuing					
E.4: Estimated net cost to the PBS/RPBS					
Net cost to PBS/RPBS ^a					
Initial					
Continuing					
E.5: Estimated net cost to health budgets (PBS/RPBS/MBS)					
Processing cost to MBS					
Net cost to government ^a					

^a Net of patient co-payments *At times, estimates presented in Section E workbook conflicts with the main body of the submission, where there are inconsistencies, Section E workbook results are presented. Source: Tables E-2 to E-5, pp163-166 of the submission and Section E worksheet accompanying the submission.

The redacted table above shows that at Year 5, the estimated number of certolizumab scripts would be 10,000 – 50,000 and the net saving to Government would be less than \$10 million.

- 6.28 The ESC advised that the estimated numbers of scripts may be inaccurate due to: (i) the assumed uptake rates for CZP (based on PBS listed CZP for a different indication); and (ii) there may be considerable uncertainty regarding the proportion of initial scripts required. The current estimates were based on GOL for PsA.
- 6.29 The submission's estimate of the cost of listing CZP for PsA may not be entirely reasonable due to omission of potential additional costs for help with injections. The lack of an auto-injector presentation for CZP would result in greater services being required for CZP administration versus ADA or ETC where an auto-injector pen is available. Patients prefer to use an auto-injector where available, as it is prescribed to the majority of patients on ADA (77%), ETC (63%).
- 6.30 The submission presented sensitivity analyses for the total cost of CZP for PsA to government, varying the assumed market growth, market share, proportion of initial scripts replaced and CZP scripts required for replacement.
- 6.31 The financial implications appeared to be most sensitive to the market uptake assumptions. Should CZP achieve equal market uptake as GOL after its listing in 2010, the savings to the government over 5 years would be \$ [REDACTED].

Financial Management – Risk Sharing Arrangements

6.32 The submission did not propose a risk share arrangement.

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required benefit listing of certolizumab for the treatment of psoriatic arthritis on the cost-minimisation basis with adalimumab, at the price proposed by the submission. The equi-effective doses are CZP 400mg at weeks 0, 2, 4 followed by 200mg every 2 weeks or 400mg every 4 weeks equals ADA 40mg every 2 weeks.
- 7.2 The PBAC noted that the submission appropriately nominated adalimumab as the main comparator and etanercept, golimumab and infliximab as the secondary comparators.
- 7.3 The PBAC noted that the submission used both a standard indirect comparison and Bayesian mixed treatment comparison (MTC) to investigate and adjust for the heterogeneity between the presented trials of RAPID-PsA (certolizumab vs. placebo), ADA1 and 2 (adalimumab vs. placebo), ETC1 and 2 (etanercept vs. placebo), GOL1 (golimumab vs., placebo), INX1 and 2 (infliximab vs. placebo) and UST1 and 2 (ustekinumab vs. placebo). The PBAC agreed with the ESC that the inclusion of ustekinumab in the Bayesian MTC analysis was not appropriate as ustekinumab was not nominated as a comparator in the submission. The PBAC also noted that the MTC results for the ACR50 at 12-16 weeks presented in the submission do not include UST.
- 7.4 The PBAC noted the ESC advice that both the standard indirect comparison and the Bayesian MTC analysis have limitations in the context of the comparison of the effectiveness of CZP with ADA and the other bDMARDs. On balance, the PBAC considered the Bayesian MTC analysis provided the most appropriate basis upon which to compare the effectiveness of the two drugs. In forming this view, the PBAC noted there is no obvious explanation for the different placebo response rates in the CZP versus other bDMARD trials. The difference in placebo events rates across the trials is substantial and therefore the Bayesian MTC is the more appropriate methodology for adjusting for both between-trial heterogeneity and uncertainty in between-trial heterogeneity across the multiple trials being compared.
- 7.5 The PBAC also noted the submission presented ACR20 at week 12 as the primary outcome and ACR20 and ACR50 at 12-16 weeks and 24 weeks and PASI75 at 24 weeks as the secondary outcomes. The PBAC agreed with the ESC that ACR50 should be considered as the primary outcome as it is more stringent than ACR20 and reflects to a greater degree the current PBS criteria for eligibility for continuing treatment with a bDMARD.
- 7.6 As such, based on the adjusted MTC result of ACR50 response at week 12-16 across treatments in anti-TNF naïve patients, the PBAC considered that CZP is non-inferior to the main comparator ADA with a relative risk (RR) of [1.09; 95%CI: ■■■, ■■■], as well as the secondary comparators ETC, GOL and INX with the respective RR of [0.84; 95% CI: ■■■, ■■■], [1.17; 95%CI: ■■■, ■■■] and [0.94;

95%CI: [REDACTED], [REDACTED]. The PBAC also noted that CZP's safety profile is not different from other TNF inhibitors.

- 7.7 The PBAC therefore accepted the submission's clinical claim that certolizumab is non-inferior to adalimumab, etanercept, golimumab and infliximab in terms of comparative effectiveness and equivalent in term of comparative safety.
- 7.8 The PBAC recommended that the Safety Net 20 Day Rule should not apply to the continuing criteria.
- 7.9 The PBAC advised that certolizumab is not suitable for prescribing by nurse practitioners.
- 7.10 The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that certolizumab and the other bDMARDs for the treatment of PsA, adalimumab, etanercept, golimumab and infliximab, should be treated as interchangeable on an individual patient basis.
- 7.11 The PBAC noted that the Authority Required PBS-listed bDMARDs for the indications of rheumatoid arthritis, psoriatic arthritis, severe active juvenile idiopathic arthritis, ankylosing spondylitis and chronic plaque psoriasis are being considered as part of the post market review for Authority Required listings.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend item:
While the requested restrictions are based on the existing restrictions for the treatment of psoriatic arthritis, they will need to be remodelled to comply with PharmCis format. The Secretariat will provide a suggested restriction in the PharmCis format as soon as it's available.

9 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.

10 Sponsor's Comment

The sponsor wishes to thank the PBAC for their evaluation.