6.03 CERTOLIZUMAB PEGOL, 200 mg/1 mL pre-filled syringe, 200 mg/1 ml syringe Cimzia®, UCB Australia

1 Purpose of Application

1.1 Section 85 Authority Required listing for certolizumab pegol (CZP) for treatment of severe chronic plaque psoriasis (CPP) in patients meeting specified PBS criteria. The PBAC has not previously considered CZP for this indication. CZP is currently reimbursed for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

1.2 The basis for the requested listing was cost minimisation versus ustekinumab (UST) and adalimumab (ADA), although the analysis presented was a cost analysis versus UST and ADA over 52 weeks of maintenance therapy (see Economic Analysis). Other biologic disease-modifying anti-rheumatic drugs (bDMARDs) currently listed on the PBS for CPP include etanercept (ETN), infliximab (IFX); secukinumab (SEC), ixekizumab (IXE), guselkumab (GUS) and tildrakizumab (TIL)[1]. Biosimilars are also available on the PBS for IFX and ETN.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with severe CPP
Intervention	Certolizumab pegol 400 mg every 2 weeks. Alternatively, a dose of 400 mg initially (Week 0) and at Weeks 2 and 4 followed by 200 mg every 2 weeks may be considered.
Comparators	Adalimumab and ustekinumab
Outcomes	PASI 75 response (and PGA 0/1 with a ≥2 improvement in PGA*) at Week 16 (CIMPASI-1 and -2); PASI 75 response at Week 12 (CIMPACT), PASI 90 responses were also reported as a secondary outcome. The submission's clinical claim was based on indirect comparisons of CZP versus UST and ADA for the outcomes PASI 75 and PASI 90.
Clinical claims	CZP 200 mg is a clinically effective treatment for CPP CZP is non-inferior in terms of both effectiveness and safety to ADA and UST

Abbreviations: ADA=adalimumab; CPP=chronic plaque psoriasis; CZP=certolizumab pegol; PGA=Physician's Global Assessment; PASI= Psoriasis Area Severity Index; UST=ustekinumab.
Source: Table 1.3, p26, 108 and 141 of the submission.
* PGA was not included in the submission's indirect comparison to support the claim of non-inferiority of CZP with UST and ADA, however, PGA was a co-primary endpoint in the CIMPASI-1 and -2 trials.

2 Requested listing

2.1 The requested restrictions were generally similar to that of currently PBS listed bDMARDs for CPP.

[1] GUS and TIL were listed on the PBS on 1 February 2019

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
CERTOLIZUMAB PEGOL 200 mg/1 mL injection, single use prefilled syringe or injection (INITIAL and CONTINUING)	1	2	5	$1,014.61#	Cimzia®, UCB Australia

Severity:	Severe
Condition:	Chronic plaque psoriasis (CPP)
Treatment phase:	Initial and continuing treatment
Restriction:	☒Authority Required - In Writing (Initial treatment) ☒Authority Required - In Writing or Telephone (Continuing treatment)
Treatment criteria:	Must be treated by a dermatologist
Clinical criteria:	Generally similar to that of currently PBS listed bDMARDs for CPP

AEMP=$952.13 (This is the current price for the other listed indications)
Source: Table 1.3, p26; Table 1.15-1.16, pp.39-46 of the submission.

2.2 The submission did not request a special pricing arrangement (SPA), however indicated that the Sponsor is willing to engage in discussions with the Department of Health regarding a potential SPA. An SPA is currently in place for the nominated comparators, ADA and UST and other bDMARDs for CPP.

2.3 CZP is administered as two 200 mg subcutaneous injections every two weeks (herein referred to as CZP 400mg). Alternatively, a dose of 400 mg initially (Week 0) and at Weeks 2 and 4 followed by 200 mg every two weeks may be considered (herein referred to as CZP 200mg)[2]. The submission requested PBS listing for both dosing regimens, however the proposed maximum quantities and number of repeats would allow up to 12 weeks of initial or continuing treatment for the CZP 400 mg dose, or up to 18 and 24 weeks of initial and continuing treatment respectively, for the CZP 200 mg dose. The initial treatment period is 28 weeks for UST, 22 weeks for IFX and 16 weeks for other bDMARDs. The continuing treatment period is 24 weeks for all other bDMARDs. The PBAC considered it was appropriate to change the number of repeats to allow 16 weeks initial and 24 weeks continuing treatment with CZP 400 mg, consistent with the recommended dose in available TGA documentation at time of consideration.

2.4 The requested PBS restriction was narrower than the proposed TGA indication with stricter criteria for prior failed therapies and disease severity. This is consistent with that for the other bDMARDs listed on the PBS.

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

3 Background

Registration status

[2] The maintenance dose of CZP for Rheumatoid arthritis (RA), Ankylosing Spondylitis(AS) and Psoriatic arthritis (PsA) is 200 mg every two weeks or 400 mg every four weeks.

3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA clinical evaluator's report and the TGA delegate's overview were available. At the time of PBAC consideration CZP was not approved by the TGA for CPP. The Advisory Committee on Medicines (ACM) advice was available prior to the PBAC meeting.

3.2 The TGA Delegate's Overview recommended approval for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The Delegate was supportive of the dosage regimen included in the draft Product Information: "The dose of Cimzia for adult patients with plaque psoriasis is 400 mg every 2 weeks. Alternatively, a dose of 400 mg initially (Week 0) and at Weeks 2 and 4 followed by 200 mg every 2 weeks may be considered."

3.3 The ACM supported the registration of CZP for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose was an initial loading dose of 400 mg every two weeks for three doses, then 200-400 mg every two weeks. The ACM noted that as there was a high degree of inter-individual variability in patient response, it was beneficial to allow a degree of flexibility in prescribing to allow clinician's to adjust dose depending on patient circumstance and response.

4 Population and disease

4.1 Psoriasis manifests as chronic inflammation of the skin, characterised by disfiguring, scaling and erythematous plaques that may be painful and severely pruritic and may cause significant reductions in quality of life (QoL). The target population proposed for CZP is the same as that for other biologics on the PBS for severe CPP. The initial treatment criteria for PBS-subsidised biologic therapy for whole body psoriasis requires patients to have a Psoriasis Area Severity Index (PASI) > 15 and have failed to achieve an adequate response, are intolerant or contraindicated to at least three (two[3]) of the four systemic therapies (methotrexate, cyclosporin and acitretin) and/or phototherapy (either PUVA or UVB).

4.2 CZP is proposed as an alternative bDMARD in the treatment of severe CPP. If listed, CZP will become one of several bDMARDs listed on the PBS for patients with severe CPP who have failed to achieve adequate response to non-biologic therapies. The addition of CZP to the clinical management algorithm is not anticipated to alter current practice. The submission suggested that CZP would mostly replace therapy with UST and ADA. However, CZP could replace any of the listed bDMARDs.

4.3 The submission highlighted CZP as the only Fc Free, PEGylated, tumour necrosis factor (TNF) inhibitor. As CZP does not bind to neonatal Fc receptor (FcRn) for IgG, it is also not expected to undergo FcRn mediated transfer across the placenta. Limited data

[3] The PBAC recommended altering the current PBS restriction so that patients are only required to have failed two of the four prior treatments (ratified Minutes to the Post-market review of the use of biologics in the treatment of severe chronic plaque psoriasis, paragraph 4.2.5, April 2018 PBAC Meeting).

support low risk for immunosuppression in the newborn and teratogenicity for this agent (TGA pregnancy Category C). CZP can be used during breastfeeding. The ESC noted that CZP may be an alternative treatment option for pregnant women as it is unlikely to cross the placenta.

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

5 Comparator

5.1 The submission nominated UST and ADA as the main comparators. The submission stated that this was based on UST and ADA being the most commonly used bDMARDs in CPP (from the DUSC report, June 2014). However, PBS statistics presented in the submission suggest SEC to be the most utilised bDMARD in 2017/2018. A comparison of CZP and SEC was not presented in the submission.

5.2 The submission acknowledged that all PBS listed biologic therapies for CPP could be substituted by CZP. Although the submission argued, as IFX is administered as a 2-hour intravenous infusion every eight weeks, that the prescription of IFX is a deliberate choice for doctors and their patients, and hence in the CZP financial model there was no replacement of IFX by CZP. Replacement for all other PBS listed bDMARDs for CPP was considered in the financial estimates.

5.3 The National Health Act 1953, Section 101(3B) stipulates that if the requested treatment is substantially more costly than alternative therapies, then the PBAC could only recommend listing at a higher price, if it is satisfied that the treatment provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the existing therapies.

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 Overall, the submission was based on 18 trials that formed the basis for two indirect comparisons versus the nominated comparators. The trial evidence included:

- three RCTs comparing CZP to placebo (PBO) (CIMPASI-1 and CIMPASI-2; results reported at 16 weeks) and active comparator ETN (CIMPACT; results reported at 12 and 16 weeks);
- nine RCTs comparing UST to either PBO or active comparator risankizumab (RIS): PHOENIX-1, PHOENIX-2, Igarashi 2012, PEARL, LOTUS. AMAGINE-2, AMAGINE-3

(results reported at 12 weeks); UltiMMa-1 and UltiMMa-2 (results reported at 12 and 16 weeks);

- six RCTs comparing ADA to PBO and GUS: CHAMPION, REVEAL, Asahina 2010, VOYAGE-1, VOYAGE-2 and X-PLORE (based on results reported at 16 weeks).

6.4 The comparisons presented in the submission were:

- an indirect comparison of CZP 200 mg versus UST based on PBO as the common reference;
- an indirect comparison of CZP 200 mg versus ADA based on PBO as the common reference.

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CZP vs PBO (and ETN)		
CIMPASI-1 (CZP_1)	Interim Clinical Study Report (CSR): An Efficacy and Safety Study of Two Dose Levels of Certolizumab Pegol (CZP) in Subjects With Plaque Psoriasis (CPP) PS0005 (CIMPASI-1).	19 Jun 2017
	Interim Clinical Study Report: A Study to Evaluate the Efficacy and Safety of Two Dose Levels of Certolizumab Pegol (CZP) in Subjects With Plaque Psoriasis (CPP). (CIMPASI-2).	21 Jun 2017
CIMPASI-2 (CZP_2)	Gottlieb A.B. Blauvelt A. Thaci D. Leonardi C.L. Poulin Y. Drew J. Peterson L. Arendt C. Burge D. Reich K. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomised, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2).	J Am Acad Dermatol 2018; 79 (2) (pp 302-314.e6)
CIMPACT (CZP_3)	Interim Clinical Study Report (CSR) Efficacy and Safety Study of Certolizumab Pegol (CZP) Versus Active Comparator and Placebo in Subjects With Plaque Psoriasis (CPP) (CIMPACT).	27 Jun 2017
	Lebwohl M. Blauvelt A. Paul C. Sofen H. Weglowska J. Piguet V. Burge D. Rolleri R. Drew J. Peterson L. Augustin M. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks of a phase 3, multicenter, randomised, double-blind, etanercept- and placebo-controlled study (CIMPACT).	J Am Acad Dermatol 2018; 79 (2) (pp 266-276.e5)
UST vs PBO		
UltIMMa-1 (UST_1)	Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials.	Lancet. 2018; 25;392(10148):650-661.
UltIMMa-2 (UST_2)		
PHOENIX 1 (UST_3)	Leonardi C, Kimball A, Papp K et al. Efficacy and safety of ustekinumab, human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 1)	Lancet 2008; 371: 1665-1674.
PHOENIX 2 (UST_4)	Papp K, Langley R, Lebwohl G et al. Efficacy and safety of ustekinumab, human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 2)	Lancet 2008; 371: 1675-1684.

Trial ID	Protocol title/ Publication title	Publication citation
Igarashi 2012 (UST_5)	Igarashi A, Kato T, Kato M et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial.	J Dermatol. 2012; 39: 242-252.
PEARL (UST_6)	Tsai T, Ho, J, Song M et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: A phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL).	J Dermatol Sci 2011; 63: 154-163.
LOTUS (UST_7)	Zhu X, Zheng M, Song M et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: Results from a phase 3 clinical trial (LOTUS).	J Drugs Dermatol. 2013; 12 (2): 166-174.
AMAGINE-2 (UST_8)	Lebwohl M, Strober B, Menter A et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis.	NEJM 2015; 373 (14): 1318-1328
AMAGINE-3 (UST_9)		
ADA vs PBO (and GUS)		
CHAMPION (ADA_1)	Saurat JH, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).	Br J Dermatol. 2008; 158(3): 558-566.
REVEAL (ADA_2)	Menter A, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial.	J Am Acad Dermatol. 2008; 58(1): 106-115.
Asahina 2010 (ADA_3)	Asahina A, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study.	J Dermatol. 2010; 37(4): 299-310.
VOYAGE-1 (ADA_4)	Blauvelt A, Papp K, Griffiths C et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial.	J Am Acad Dermatol. 2017; 76: 405-417.
VOYAGE-2 (ADA_5)	Reich K, Armstrong A, Foley P et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator controlled VOYAGE 2 trial.	J Am Acad Dermatol. 2017; 76: 418-431.
X-PLORE (ADA_6)	Gordon KB, Duffin KC, Bissonnette R, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis.	N Engl J Med. 2015; 9;373(2):136-44

Abbreviations: ADA=adalimumab, CZP=certolizumab pegol; ETN-etanercept, PBO=placebo, UST=ustekinumab.
Note: only main trial citations have been included in this table.
Source: Tables 2.3 – 2.5; p58-60 of the submission.

6.6 The key features of the included trials are summarised in Table 3.

Table 3: Key features of evidence included in the submission

Trial	N	Design/ duration of follow-up	Within trial ROB	Patient population	Key Outcomes
CZP vs PBO					
CZP_1 (CIMPASI-1)	234	R, DB, MC, 48 wks. PBO patients crossed over to CZP 200 mg (≥50 PASI responders<70) or 400 mg (PASI 50 non-responders) at Wk 16.	Low	Moderate to severe CPP; PGA≥3, PASI score ≥12, BSA≥10%	PASI 75 & PGA 0/1 & ≥2-point improvement in PGA [and PASI 90] at Wk 16.
CZP_2 (CIMPASI-2)	227				
CZP_3 (CIMPACT)	559	R, DB, MC, 48 wks. PBO patients (PASI 75 non-responders) crossed over to CZP 400 mg at Wk 16.Included active comparator ETN.	Low		PASI 75 and [PASI 90] at Wk 12.
UST vs PBO					
UST_1 (UltIMMa-1)	506	R, DB, MC, 52 wks. Trial compared RIS, UST and PBO. PBO patients crossed over to RIS at Wk 16.	Low	Moderate to severe CPP; sPGA≥3, PASI score ≥12, BSA≥10%	PASI 90 & sPGA (0,1) at Wk 16 [and PASI 75 at Wk 12].
UST_2 (UltIMMa-2)	491		Low		
UST_3 (PHOENIX 1)	766	R, DB MC, 40 wks. PBO patients crossed-over to UST at Wk 12. Wk 40 to 72: randomised withdrawal phase [a]	Low	Moderate to severe CPP; PASI score ≥12, BSA≥10%	PASI 75 [and PASI 90] at Wk 12. Maintenance of PASI response to trial end.
UST_4 (PHOENIX 2)	1230	R, DB, MC, 28 wks, PBO patients crossed-over to UST at Wk 12. Wk28 -52: randomised dose intensification phase.	Low		
UST_5 (Igarashi 2012)	158	R, DB, MC, 72 wks (efficacy results to 64 wks), PBO patients crossed-over to UST at Wk 12.	Low	Same as UST_3 and UST_4, but in Japanese pts	
UST_6 (PEARL)	121	R, DB, MC, 36 wks (efficacy results to 28 wks). PBO patients crossed-over to UST at Wk 12.	Low	Same as UST_3 and UST_4, but in Korean or Taiwanese pts	
UST_7 (LOTUS)	322	R, DB, MC, 36 wks (efficacy results to 28 wks). PBO patients crossed-over to UST at Wk 12.	Low	Same as UST_3 and UST_4, but in Chinese pts	
UST_8 (AMAGINE-2)	1831	R, DB, MC, 52 wks. Trial compared BRO, UST and PBO. PBO patients crossed-over to BRO at Wk 12.	Low	Moderate to severe CPP; PASI score ≥12, BSA≥10%, sPGA≥3	PASI 75 & sPGA (0,1) at Wk 12. Maintenance of PASI response to Wk 52.
UST_9 (AMAGINE-3)	*1881*		*Low*		
ADA vs PBO					
ADA_1 (CHAMPION)	271	R, DB, MC, 16wks	Low	Moderate to severe; PASI score≥10, BSA≥10%	PASI 75, [PASI 90] at Wk 16
ADA_2 (REVEAL)	1,212	R, DB, MC, 52wks. PBO patients crossed over to ADA at Wk 16.	Low	Moderate to severe; PASI score≥12, PGA≥3, BSA≥10%	PASI 75 at Wk 16 [PASI 90 at Wk 12]
ADA_3 (Asahina 2010)	235	R, DB, MC, 24wks	Low	Moderate to severe; PASI score≥12, BSA≥10%; Japanese pts	PASI 75 at Wk 16
ADA_4 (VOYAGE-1)	837	R, DB, MC, 48 wks. PBO patients crossed over to GUS at Wk 16. Switching not permitted for ADA group.	Low	Moderate to severe CPP; IGA≥3, PASI score ≥12, BSA≥10%	PASI 90 & IGA 0/1 [and PASI 75] at Wk 16
ADA_5 (VOYAGE-2)	992	R, DB, MC, 28 wks PBO patients crossed over to GUS at Wk 16.	Low		
ADA_6 X-PLORE	293	R, DB, MC, 52wks. Phase 2 dose ranging trial of GUS compared to ADA and PBO. PBO patients crossed over to GUS at Wk 16.	Low	Moderate to severe CPP; PGA≥3, PASI score ≥12, BSA≥10%	PGA 0/1[and PASI 75] at Wk 16

Abbreviations: ADA=adalimumab; BRO=brodalumab; BSA=body surface area; CPP=chronic plaque psoriasis; DB=double blind; ETN=etanercept; IGA=investigator's global assessment; MC=multicentre; PASI=Psoriasis Area Severity Index; PC=placebo control, pts=patients; R=randomised; PGA=physician's global assessment; RIS=risankizumab; ROB=risk of bias; sPGA=static physician global assessment; UST=ustekinumab [ ] indicate this was a reported outcome used in the indirect comparison although not primary for the trial.

[a] UST patients who attained PASI 75 were re-randomised to withdrawal or continuing treatment and PBO group patients switched back to PBO. Patients could restart treatment if lost at least PASI 50 response.

Source: compiled during the evaluation from trial publications.

6.7 All trials were multicentre, placebo-controlled, double-blind RCTs. Overall, the risk of bias in the placebo-controlled phase of the trials was low. As most of the trials allowed patients to switch from PBO to active treatment beyond the initial placebo-controlled phase (12/16 weeks), outcomes from subsequent periods would be subject to bias. However, appropriately, trial outcomes were assessed at the end of the placebo-controlled periods.

6.8 Key inclusion criteria across the CZP, UST and most of the ADA trials were similar, recruiting adult patients with moderate to severe plaque psoriasis (PASI score > 12, and body surface area involvement > 10%). CHAMPION (ADA_1) permitted inclusion of patients with a PASI score > 10 however, the mean participant PASI score was approximately 19-20, which was in the range of the other trials (19-30).

6.9 The CZP trials, four UST trials (UltIMMa-1 and -2, and AMAGINE 2 and 3) and two ADA trials (REVEAL and X-PLORE) required patients to have a Physician's Global Assessment (PGA) score > 3. Another two ADA trials (VOYAGE-1 and -2) required patients to have an Investigator's Global Assessment (IGA) score > 3. However, the CZP trials used a five-point PGA scale that ranged from 0 to 4, whereas the other trials reporting the PGA score used a six-point scale that ranged from 0 to 5. In both cases, a score of 0 indicated clear symptoms/no disease and greater scores indicated more severe disease. The IGA scoring was as follows: cleared (0), minimal (1), mild (2), moderate (3), or severe (4) symptoms. In all trials, patients were required to have moderate or severe CPP.

6.10 The CZP, UST and ADA trial populations differed to the requested PBS population (which has stricter requirements for number of prior failed therapies and severity), but overall the trial populations were similar to other trials of bDMARDs previously considered by the PBAC and were generally representative of the likely PBS population.

6.11 The dosing regimens of CZP and ADA in the trials were consistent with those recommended in the respective (draft) Product Information (PI). The submission inappropriately excluded the CZP 400 mg dose when conducting the indirect comparisons versus UST and ADA. The submission provided no justification for excluding the CZP 400 mg dose. For UST, except for the UltIMMa and AMAGINE trials, which administered UST based on the recommended weight based dosing (45 mg for patients ≤ 100 kg and 90 mg for patients >100 kg), the doses used generally deviated from its PI, as patients were randomly allocated to receive either the 45 mg or 90 mg dose.

Comparative effectiveness

6.12 The PBAC had previously based recommendations for listing of bDMARDs for the treatment of CPP on the proportion of patients i) achieving and ii) maintaining a PASI 75 response (≥75% improvement from baseline in the Psoriasis Area and Severity Index score). This is also consistent with the PBS eligibility criteria for continuation treatment.

6.13 The PASI 75 response was the primary outcome in the included trials except the UltIMMa ($UST_{1 \text{ and } 2}$) and VOYAGE ($ADA_{4 \text{ and } 5}$) trials, for which PASI 90 (≥90% improvement from baseline in the PASI score) was the primary outcome, and X-PLORE (ADA_6), for which PGA was the primary outcome. Other efficacy endpoints across the trials included PASI 100 (100% improvement from baseline in PASI score) and the Dermatology Life Quality Index (DLQI). Appropriately, the submission's clinical claims were based on the PASI 75 and PASI 90 outcomes.

6.14 Tables 4 – 6 summarise the direct and indirect comparative results of the PASI 75 and PASI 90 responses for CZP versus the nominated comparators, based on the results for the ITT populations at either 12 or 16 weeks:

A. direct comparisons of CZP vs ETN from CIMPACT;

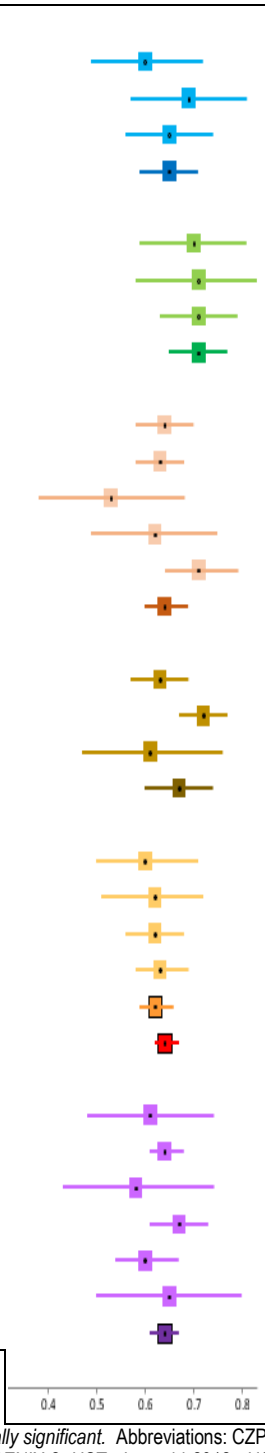
B. indirect comparisons for CZP vs UST via the common reference of PBO; and

C. indirect comparisons for CZP vs ADA via the common reference of PBO.

6.15 The submission inappropriately only presented results of the indirect comparison of the CZP 200 mg dose versus the comparators, and did not conduct an indirect comparison for the CZP 400 mg dose. Additional analyses for the CZP 400mg dose were conducted during the evaluation and are summarised below. The submission also included REVEAL (ADA_2) for the PASI 90 analyses, and used results at Week 24 (only week 12 or 24 results were available for PASI 90). This was inconsistent with time-points elected by the submission for the assessment of outcomes from the other trials and therefore was excluded from the analyses conducted during the evaluation.

Table 4: PASI 75 response at Weeks 12/16 across the trials – ITT populations

Trial	Drug n[a]/N (%)	Control n[a]/N (%)	OR (95% CI)^	*RD (95% CI)^*	*NNT (95%CI)*
CZP 200mg vs PBO Wk 16					
CZP_1	63/95 (66.5)	3/51 (6.5)	**31.50 (9.10, 109.02)**	***0.60 (0.49, 0.72)***	*2 (1,2)*
CZP_2	74/91 (81.4)	6/49 (11.6)	**31.20 (11.43, 85.12)**	***0.69 (0.57, 0.81)***	*1 (1, 2)*
CZP_3	113/165 (68.2)	2/57 (3.8)	**59.76 (14.04, 254.41)**	***0.65 (0.56, 0.74)***	*2 (1, 2)*
Pooled	250/351 (*74.5*[b])	11/157 (7.5[b])	**36.22 (18.22, 72.00)**	***0.65 (0.59, 0.71)***	*2, (1, 2)*
CZP 400mg vs PBO Wk 16					
CZP_1	*67/88 (75.8)*	*3/51 (6.5)*	***51.05 (14.40, 180.91)***	***0.70 (0.59, 0.81)***	*1 (1, 2)*
CZP_2	*72/87 (82.6)*	*6/49 (11.6)*	***34.40 (12.41, 95.33)***	***0.71 (0.58, 0.83)***	*1 (1,2)*
CZP_3	*125/167 (74.7)*	*2/57 (3.8)*	***81.85 (19.13, 350.15)***	***0.71 (0.63, 0.79)***	*1 (1, 2)*
Pooled	*264/342 (80.1[b])*	*11/157 (7.5[b])*	***47.32 (23.57, 94.96)***	***0.71 (0.65, 0.77)***	*1 (1, 2)*
UST 45mg vs PBO Wk 12					
UST_3	171/255 (67.1)	8/255 (3.1)	**62.85 (29.66, 133.19)**	***0.64 (0.58, 0.70)***	*2 (1, 2)*
UST_4	273/409 (66.7)	15/410 (3.7)	**52.86 (30.34, 92.09)**	***0.63 (0.58, 0.68)***	*2 (1, 2)*
UST_5	38/64 (59.4)	*2/32[#] (6.3)*	***21.92 (4.82, 99.82)***	***0.53 (0.38, 0.68)***	*2 (1, 2)*
UST_6	41/61 (67.2)	3/60 (5.0)	**38.95 (10.85, 139.83)**	***0.62 (0.49, 0.75)***	*2 (1, 2)*
UST_7	132/160 (82.5)	18/162 (11.1)	**37.71 (19.94, 71.34)**	***0.71 (0.64, 0.79)***	*1 (1, 2)*
Pooled	655/949 (69.0)	*46/919* (5.0)	***46.50 (33.01, 65.49)***	***0.64 (0.60, 0.69)***	*2 (1, 2)*
UST 90mg vs PBO Wk 12					
UST_3	170/256 (66.4)	8/255 (3.1)	**61.03 (28.82, 129.25)**	***0.63 (0.57, 0.69)***	*2 (1, 2)*
UST_4	311/411 (75.7)	15/410 (3.7)	**81.90 (46.66, 143.76)**	***0.72 (0.67, 0.77)***	*1 (1, 1)*
UST_5	42/62 (67.7)	*2/32[#] (6.3)*	***31.50 (6.84, 145.06)***	***0.61 (0.47, 0.76)***	*2 (1, 2)*
Pooled	523/729 (71.7)	*25/697 (3.6)*	***68.83 (44.70, 106.01)***	***0.67 (0.60, 0.74)***	*1 (1, 2)*
UST Label vs PBO Wk 12					
UST_1	70/100 (70.00)	10/102 (9.80)	**21.47 (9.84, 46.84)**	***0.60 (0.50, 0.71)***	*2 (1, 2)*
UST_2	69/99 (69.70)	8/98 (8.16)	**25.88 (11.16, 59.97)**	***0.62 (0.51, 0.72)***	*2 (1, 2)*
UST_8	210/300 (70.0)	25/309 (8.1)	**26.51 (16.44, 42.74)**	***0.62 (0.56, 0.68)***	*2 (1, 2)*
UST_9	217/313 (69.3)	19/315 (6.0)	**35.21 (20.89, 59.37)**	***0.63 (0.58, 0.69)***	*2 (1, 2)*
Pooled	566/812 (69.7)	62/824 (7.5)	**28.13 (20.84, 37.98)**	***0.62 (0.59, 0.66)***	*2 (2, 2)*
Pooled UST (all)	*1744/2490 (70.0)*	*133/2440 (5.5)*	***40.29 (30.95, 52.45)***	***0.64 (0.62, 0.67)***	*2 (1, 2)*
ADA 40 mg eow vs PBO Wk 16					
ADA_1	86/108 (79.6)	10/53 (18.9)	**16.81 (7.31, 38.64)**	***0.61 (0.48, 0.74)***	*2 (1, 2)*
ADA_2	578/814 (71.0)	26/398 (6.5)	**35.04 (22.90, 53.62)**	***0.64 (0.61, 0.68)***	*2 (1, 2)*
ADA_3	27/43 (62.8)	2/46 (4.3)	**37.13 (7.91, 174.23)**	***0.58 (0.43, 0.74)***	*2 (1, 2)*
ADA_4	244/334 (73.05)	10/174 (5.75)	**44.46 (22.47, 87.99)**	***0.67 (0.61, 0.73)***	*1 (1, 2)*
ADA_5	170/248 (68.55)	20/248 (8.06)	**24.85 (14.63, 42.21)**	***0.60 (0.54, 0.67)***	*2 (1, 2)*
ADA_6	30/43 (69.77)	2/42 (4.76)	**46.15 (9.68, 220.11)**	***0.65 (0.50, 0.80)***	*2 (1, 2)*
Pooled	1135/1590 (71.4)	70/961 (7.3)	**31.04 (23.65, 40.75)**	***0.64 (0.61, 0.67)***	*2 (1, 2)*



Grey shading=data previously seen by the PBAC. Italics=results estimated during evaluation. Bold=statistically significant. Abbreviations: CZP_1=CIMPASI-1; CZP_2=CIMPASI-2; CZP_3=CIMPACT; UST_1=UltIMMa-1; UST_2=UltIMMa-2; UST_3=PHOENIX-1; UST_4=PHOENIX-2; UST_5=Igarashi 2012; UST_6=PEARL; UST_7=LOTUS; UST_8=AMAGINE-2; UST_9=AMAGINE-3; ADA_1=CHAMPION; ADA_2=REVEAL; ADA_3=Asahina 2010; ADA_4=VOYAGE-1; ADA_5=VOYAGE-2; ADA_6=X-PLORE; UST Label=(45 mg for patients≤100 kg; 90 mg for patients>100 kg); Wk=week; ADA=adalimumab; CZP=certolizumab pegol; ETN=etanercept; PBO=placebo, UST=ustekinumab, PASI 75= ≥ 75%reduction in the Psoriasis Area and Severity Index. ^ estimated during evaluation using random effects meta-analysis (RevMan V5.3). #ITT population: one patient in the PBO arm was randomised but did not receive active treatment.

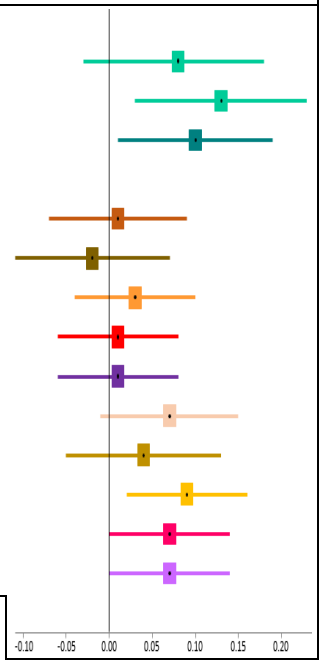
[a] The CZP trials reported only responder rates, rather than number of responders. Therefore, the "n" presented for the CZP trials were derived from the responder rates, rounded to the nearest integer.

[b] Sourced from Figure 1a, p4 of Blauvelt A, Reich K, Lebwohl M, et al. Certolizumab pegol for the treatment of patients with moderate-to-severe chronic plaque psoriasis: pooled analysis of week 16 data from three randomized controlled trials. J Eur Acad Dermatol Venereol. 2018 Sep 22.

Source: constructed during the evaluation using results reported in CSRs accompanying the submission, and published papers of trials.

Table 5: Results of direct and indirect comparisons of CZP 200 mg and CZP 400 mg versus comparators for PASI 75

Direct or Indirect comparisons		OR (95% CI)^	*RD (95% CI)^*
Direct: CZP vs ETN Wk 12[a] (CIMPACT, CZP3)			
CZP 200mg	vs ETN	*1.37 (0.89, 2.12)*	*0.08 (-0.03, 0.18)*
CZP 400mg	vs ETN	***1.72 (1.11, 2.67)***	***0.13 (0.03, 0.23)***
Pooled CZP	vs ETN	***1.53 (1.05, 2.23)***	***0.10 (0.01, 0.19)***
Indirect: CZP vs UST & ADA via PBO as common comparator			
CZP 200 mg	vs UST 45 mg	0.78 (0.36, 1.68[b])	*0.01 (-0.07, 0.09)*
	vs UST 90 mg	0.53 (0.23, 1.18[b])	*-0.02 (-0.11, 0.07)*
	vs UST label	1.29 (0.61, 2.73)	*0.03 (-0.04, 0.10)*
	vs UST all	0.90 (0.43, 1.88)	*0.01 (-0.06, 0.08)*
	vs ADA	1.17 (0.56, 2.44)	*0.01 (-0.06, 0.08)*
CZP 400 mg	*vs UST 45 mg*	*1.02 (0.47, 2.21)*	*0.07 (-0.01, 0.15)*
	vs UST 90 mg	*0.69 (0.30, 1.56)*	*0.04 (-0.05, 0.13)*
	vs UST label	*1.68 (0.79, 3.59)*	***0.09 (0.02, 0.16)***
	vs UST all	*1.17 (0.56, 2.47)*	*0.07 (0.00, 0.14)*
	vs ADA	*1.52 (0.72, 3.22)*	*0.07 (0.00, 0.14)*



Abbreviations: ADA=adalimumab, CZP=certolizumab pegol; UST=ustekinumab, PASI 75= ≥75% reduction in the Psoriasis Area and Severity Index; UST Label refers to weight-based dosing for UST (UST 45 mg for patients ≤ 100 kg; UST 90 mg for patients > 100 kg). Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. ^estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

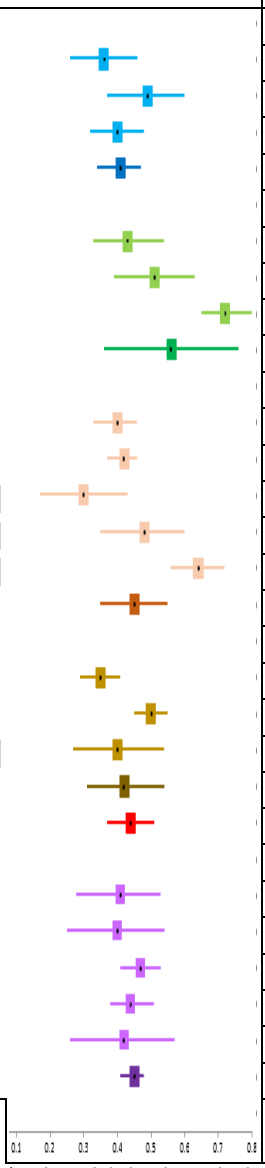
[a] Calculated during evaluation based on deriving the number of responders from the reported proportion of responders from the CIMPACT CSR. Therefore, there is a slight variance from the published ORs in the CIMPACT paper (Lebwohl et al 2018), which reported OR 95% CI: 1.4 (0.9, 2.2) and 1.8 (1.1, 2.8) for the CZP 200 mg and 400 mg versus ETN respectively. This does not have a significant impact on the overall results.

[b] A slight variance exists between the Commentary CI and that presented in the submission due to a small difference in number of patients in the placebo pool included in the ITT analyses (refer to # in Table 4 footnotes).

Source: constructed during the evaluation using results reported in CSRs accompanying the submission, and published papers of trials.

Table 6: PASI 90 response at Weeks 12/16 across the trials – ITT populations

Trial	Drug n[a]/N (%)	Control n[a]/N (%)	OR (95% CI)^	*RD (95% CI)^*	*NNT (95%CI)*
CZP 200mg vs PBO Wk 16					
CZP_1	34/95 (35.8)	0/51 (0.4)	**57.78 (3.46, 965.76)**	**0.36 (0.26, 0.46)**	*3 (2, 4)*
CZP_2	48/91 (52.6)	2/49 (4.5)	**26.23 (6.01, 114.52)**	**0.49 (0.37, 0.60)**	*2 (2, 3)*
CZP_3	66/165 (39.8)	0/57 (0.3)	**76.86 (4.67, 1265.30)**	**0.40 (0.32, 0.48)**	*3 (2, 3)*
Pooled	148/351 *(44.5[b])*	2/157 *(1.6[b])*	**36.54 (11.19, 119.32)**	**0.41 (0.34, 0.47)**	*2 (2, 3)*
CZP 400mg vs PBO Wk 16					
CZP_1	*38/88 (43.6)*	0/51 (0.4)	**78.52 (4.70, 1312.95)**	**0.43 (0.33, 0.54)**	*2, (2, 3)*
CZP_2	*48/87 (55.4)*	2/49 (4.5)	**28.92 (6.60, 126.65)**	**0.51 (0.39, 0.63)**	*2 (2, 3)*
CZP_3	*121/167 (72.3)*	*0/57 (0.3)*	**300.48 (18.19, 4962.52)**	**0.72 (0.65, 0.80)**	*1 (1, 2)*
Pooled	*207/342 (52.2[b])*	*2/157 (1.6[b])*	**59.24 (14.60, 240.34)**	**0.56 (0.36, 0.76)**	*2, (1, 3)*
UST 45mg vs PBO Wk 12					
UST_3[d]	106/255 (41.6)	5/255 (2.0)	**35.57 (14.18, 89.22)**	**0.40 (0.33, 0.46)**	*3 (2, 3)*
UST_4[d]	173/409 (42.3)	3/410 (0.7)	**99.45 (31.41, 314.89)**	**0.42 (0.37, 0.46)**	*2 (2, 3)*
UST_5	21/64 (32.8)	1/32[#] (3.1)	**15.14 (1.93, 118.61)**	**0.30 (0.17, 0.43)**	*3 (2, 6)*
UST_6	30/61 (49.2)	1/60 (1.7)	**57.10 (7.43, 438.78)**	**0.48 (0.35, 0.60)**	*2 (2, 3)*
UST_7	107/160 (66.9)	5/162 (3.1)	**63.39 (24.53, 163.80)**	**0.64 (0.56, 0.72)**	*2, (1, 2)*
Pooled	437/949 (46.0)	15/919 (1.6)	**51.86 (30.43, 88.36)**	**0.45 (0.35, 0.55)**	*2 (2, 3)*
UST 90mg vs PBO Wk 12					
UST_3[d]	94/256 (36.7)	5/255 (2.0)	**29.01 (11.55, 72.87)**	**0.35 (0.29, 0.41)**	*3, (2, 3)*
UST_4[d]	209/411 (50.9)	3/410 (0.7)	**140.37 (44.35, 444.24)**	**0.50 (0.45, 0.55)**	*2, (2, 2)*
UST_5	27/62 (43.5)	1/32[#] (3.1)	**23.91 (3.07, 186.44)**	**0.40 (0.27, 0.54)**	*3, (2, 4)*
Pooled	330/729 (45.3)	9/697 (1.3)	**49.78 (15.02, 164.97)**	**0.42 (0.31, 0.54)**	*2, (2, 3)*
Pooled $UST_{3,4,5,6,7}$	*767/1678 (45.7)*	*24/1616 (1.5)*	**50.97 (31.57, 82.31)**	**0.44 (0.37, 0.51)**	*2 (2, 3)*
ADA 40 mg eow vs PBO Wk 16					
ADA_1	56[c]/108 (51.9)	6/53 (11.3)	**8.44 (3.33, 21.38)**	**0.41 (0.28, 0.53)**	*2 (2, 4)*
ADA_3	17/43 (39.5)	0/46 (0)	**61.42 (3.55, 1063.13)**	**0.40 (0.25, 0.54)**	*3 (2, 4)*
ADA_4	166/334 (49.7)	5/174 (2.9)	**33.40 (13.38, 83.38)**	**0.47 (0.41, 0.53)**	*2, (2, 2)*
ADA_5	116/248 (46.8)	6/248 (2.4)	**35.44 (15.19, 82.72)**	**0.44 (0.38, 0.51)**	*2 (2, 3)*
ADA_6	19/43 (44.2)	1/42 (2.4)	**32.46 (4.08, 258.00)**	**0.42 (0.26, 0.57)**	*2 (2, 4)*
Pooled	374/776 (48.2)	18/563 (3.2)	**24.05 (11.85, 48.81)**	**0.45 (0.41, 0.48)**	*2 (2, 2)*



Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. ^ estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3. Abbreviations: CZP_1=CIMPASI-1; CZP_2=CIMPASI-2; CZP_3=CIMPACT; UST_1=UltIMMa-1; UST_2=UltIMMa-2; UST_3=PHOENIX-1; UST_4=PHOENIX-2; UST_5=Igarashi 2012; UST_6=PEARL; UST_7=LOTUS; UST_8=AMAGINE-2; UST_9=AMAGINE-3; ADA_1=CHAMPION; ADA_3=Asahina 2010; ADA_4=VOYAGE-1; ADA_5=VOYAGE-2; ADA_6=X-PLORE; UST Label refers to weight-based dosing for UST (UST 45 mg for patients ≤ 100 kg; UST 90 mg for patients > 100 kg); Wk=week; ADA=adalimumab, CZP=certolizumab pegol; ETN=etanercept; PBO=placebo, UST=ustekinumab, PASI 75= ≥75% reduction in the Psoriasis Area and Severity Index. #analysis in the ITT population. One patient in the PBO arm was randomised but did not receive active treatment.

[a] The CZP trials reported only responder rates, rather than number of responders. Therefore, the "n" presented for the CZP trials were derived from the responder rates, rounded to the nearest integer.

[b] Sourced from Figure 1c, p4 of Blauvelt A, Reich K, Lebwohl M, et al. Certolizumab pegol for the treatment of patients with moderate-to-severe chronic plaque psoriasis: pooled analysis of week 16 data from three randomized controlled trials. J Eur Acad Dermatol Venereol. 2018 Sep 22. doi: 10.1111/jdv.15258.

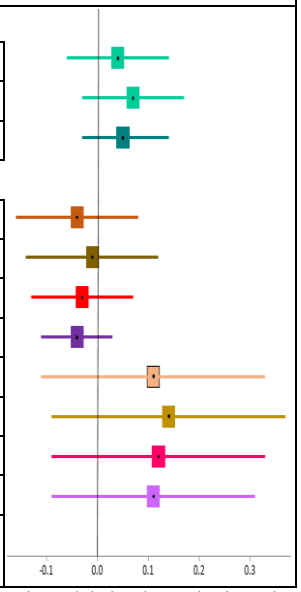
[c] The CHAMPION publication reported results as bar graphs, with the proportion of responders in text that was too small to be clear, both in the PDF accompanying the submission and in the online search conducted during evaluation. The evaluation interpreted the writing as 51.9%, which equated to 56 patients. The submission used 55 patients in its analyses. This has minimal impact on the overall results.

[d] Obtained from publications for the Pheonix 1 and 2 trials reported for combined 45mg and 90mg dosages. The guselkumab March 2017 PSD indicated that in the guselkumab submission IPD data were supplied by the submission (for subgroups of patients in the trial who received the TGA approved UST dose: 45mg for patients weighing ≤ 100 kg and UST 90 mg for patients weighing > 100 kg), however as those results had been redacted in the PSD, they are not able to be used in this evaluation.

Source: constructed during the evaluation using results reported in CSRs accompanying the submission, and published papers of trials.

Table 7: Results of the indirect comparison of CZP 200 mg and CZP 400 mg versus UST and ADA for PASI 90

Indirect comparison via PBO		OR (95% CI)^	*RD (95% CI)^*
Direct comparison CZP vs ETN Wk 12 (CIMPACT, CZP3)			
CZP 200mg	vs ETN	1.21 (0.75, 1.93)	0.04 (-0.06, 0.14)
CZP 400mg	vs ETN	1.40 (0.88, 2.23)	0.07 (-0.03, 0.17)
Pooled CZP	vs ETN	1.30 (0.86, 1.96)	0.05 (-0.03, 0.14)
Indirect comparisons CZP versus UST and ADA via PBO as common comparator			
CZP 200 mg	vs UST 45 mg	0.70[a] (0.19, 2.58)	*-0.04 (-0.16, 0.08)*
	vs UST 90 mg	0.73[a] (0.14, 3.95)	*-0.01 (-0.14, 0.12)*
	vs UST pooled	0.72 (0.20, 2.57)	*-0.03 (-0.13, 0.07)*
	vs ADA	*1.52 (0.38, 6.03)*	*-0.04 (-0.11, 0.03)*
CZP 400 mg	*vs UST 45 mg*	*1.14 (0.26, 5.11)*	*0.11 (-0.11, 0.33)*
	vs UST 90 mg	*1.19 (0.19, 7.52)*	*0.14 (-0.09, 0.37)*
	vs UST pooled	*1.16 (0.26, 5.11)*	*0.12 (-0.09, 0.33)*
	vs ADA	*2.46 (0.51, 11.83)*	*0.11 (-0.09, 0.31)*



Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. ^estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.
Abbreviations: ADA=adalimumab, CZP=certolizumab pegol; UST=ustekinumab, PASI 75= ≥75% reduction in the Psoriasis Area and Severity Index
[a] A slight variance exists between the Commentary OR and that presented in the submission due to a small difference in number of patients in the placebo pool included in the ITT analyses (refer to # in Table 6 footnotes)
Source: constructed during the evaluation using results reported in CSRs accompanying the submission, and published papers of trials.

Summary of efficacy results

CZP versus ETN (direct evidence from CIMPACT)

6.16 The CZP 400 mg (and the pooled CZP 200 mg and 400 mg) groups had significantly greater proportions of PASI 75 responders than the ETN group at Week 12 (risk difference [RD] 95% confidence interval [CI]: [0.13; 0.03, 0.23] and [0.10; 0.01, 0.19] respectively). Results for CZP 200 mg however, showed no significant differences in the PASI 75 response versus ETN (RD 95% CI: 0.08; -0.03, 0.18). For the PASI 90 outcome, although both CZP 200 mg and 400 mg groups had numerically greater proportions of responders compared to the ETN group, the differences were not statistically significant.

CZP versus UST (indirect evidence)

6.17 Both CZP and UST were significantly more effective than PBO in terms of proportions of patients attaining the PASI 75 and PASI 90 response at Week 16 and Week 12, respectively.

6.18 Results of the indirect comparisons using PBO as common reference indicated that CZP 200mg and CZP 400 mg were not significantly different to UST for attainment of the PASI75 and PASI 90 response for the initial treatment phase, with only the comparison of CZP 400 mg versus UST label reaching statistical significance (RD 95% CI: 0.09; 0.02-0.16). Of note, the PASI 75 and PASI 90 responder rates were measured at 16 weeks in the CZP trials and 12 weeks in the UST trials. This may bias the results in favour of CZP, as CZP patients may have higher response rates due to a longer duration of treatment. More UST patients are expected to attain a PASI 75 response beyond Week 12; this is also reflected in the UST PBS restriction, which require assessment of response after a minimum of 12 weeks of treatment, but allows for up to 28 weeks of initial treatment.

CZP versus ADA

6.19 Both CZP and ADA were significantly more effective than PBO in terms of proportions of patients attaining the PASI 75 and PASI 90 response at Week 16. Based on indirect comparisons using PBO as common reference, no significant differences were observed between CZP 200mg or CZP 400mg and ADA with respect to the PASI 75 or PASI 90 response, however a conclusion of non-inferiority of CZP versus ADA may be reasonable.

Comparative harms

6.20 A summary of treatment emergent adverse events (TEAEs) from the CZP trials during the placebo-controlled phase (Weeks 0 to 16) is presented in Table 8.

Table 8: Summary of key adverse events in the CZP trials (placebo-controlled phase)

Event, n (%)	CZP 200 mg (N=350)	CZP 400 mg (N=342)	CZP pooled (N=692)	ETN (N=168)	PBO (N=157)
Any TEAE	197 (56.3)	217 (63.5)	414 (59.8)	78 (46.4)	97 (61.8)
Serious TEAEs	5 (1.4)	16 (4.7)	21 (3.0)	1 (0.6)	7 (4.5)
Discontinuations due to TEAEs	4 (1.1)	4 (1.2)	8 (1.2)	4 (2.4)	0
Drug-related TEAEs	45 (12.9)	54 (15.8)	99 (14.3)	20 (11.9)	20 (12.7)
Severe TEAEs	8 (2.3)	13 (3.8)	21 (3.0)	5 (3.0)	8 (5.1)
Infections and infestations	108 (30.9)	124 (36.3)	232 (33.5)	NR	53 (33.8)
Deaths	0	0	0	0	0

Abbreviations: CZP=certolizumab pegol; n=number of subjects who reported at least 1 TEAE in the category; NR=not reported; PBO=placebo; TEAE=treatment-emergent adverse event

Source: Table 2.52, p112 of the submission, Tables 5-5 and 5-7, p53, 56 of "Section 2.5 – Clinical Overview" accompanying the submission

6.21 Although the incidence of any TEAEs and serious TEAEs were higher in the CZP 400 mg group compared to the CZP 200 mg group, rates in both groups were comparable to

that in the pooled PBO arms across the CZP trials. Severe TEAEs were higher in the PBO group compared to both CZP groups. The incidence of infections and infestations were similar across all groups. No deaths occurred during the placebo-controlled phase of the trials and there were few discontinuations due to TEAEs across the CZP groups.

6.22 A summary of TEAEs in the maintenance phase of the CZP trials, and indirect comparisons of safety of CZP versus UST and ADA were also presented by the submission. The incidence of any TEAE, serious TEAEs, severe TEAEs, related TEAEs, and TEAEs leading to discontinuation during the maintenance treatment period were similar in the CZP 400mg and CZP 200mg groups. Overall, results of the submission's indirect comparisons did not indicate any significant differences between CZP 200mg, UST and ADA for the adverse events compared. Additional analyses conducted during the evaluation for CZP 400mg versus ADA also indicated no significant differences for any TEAEs, serious TEAEs, discontinuations and infections.

Clinical claim

6.23 The submission described CZP as non-inferior in terms of effectiveness and safety compared to UST and ADA. Based on the evidence presented in the submission (for CZP 200 mg) and analyses conducted during evaluation (for CZP 400 mg), both CZP 200 mg and 400 mg appeared to be non-inferior in terms of effectiveness and safety compared to UST and ADA. The Pre Sub-Committee Response (PSCR) stated it is not reasonable to expect that patients will use CZP 400 mg and that the majority of patients will be treated with CZP 200 mg. The PSCR indicated CZP 400 mg is used in Germany in approximately 10 to 15% patients. However the ESC noted that the dosage recommendation in the EU is a loading dose of 400 mg at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks with a dose increase to 400 mg every 2 weeks in patients with insufficient response[4]. The ESC noted that CZP 400 mg was the recommended dose in the draft Product Information provided with the submission and considered that the clinical claim should be based on this dose. The Pre-PBAC Response argued the ACM advice indicated the evidence was not sufficient to demonstrate a statistically significant difference in efficacy between 200 mg and 400 mg dosing regimens, however as the 400 mg dose was associated with more adverse events it was inconceivable that 400 mg would be the most commonly prescribed dose. The PBAC noted the dose supported by the TGA Delegate (400 mg every 2 weeks) was different from the dose recommended by the ACM (200-400 mg every 2 weeks) (see paragraphs 3.3 and 3.4).

6.24 The PBAC considered the claim of non-inferior comparative effectiveness for CZP 200 mg vs UST and ADA was adequately supported. The PBAC also considered CZP 400 mg was of non-inferior comparative effectiveness vs UST and ADA based on the data presented during evaluation.

[4] Page 29 of TGA Delegate's Overview

6.25 The PBAC considered the claim of non-inferior comparative safety for CZP 200 mg vs UST and ADA was reasonable. The PBAC also considered CZP 400 mg was of non-inferior comparative safety vs UST and ADA based on the data presented during evaluation.

Economic analysis

6.26 The submission presented a cost analysis comparing CZP 200 mg with UST and ADA. This approach was not reasonable, as it implicitly allowed CZP 400 mg to be more costly than CZP 200 mg and hence also the nominated comparators. No evidence was presented in the submission to demonstrate CZP 400 mg to be superior to the nominated comparators. Rather, indirect comparisons conducted for CZP 400 mg versus UST and ADA during the evaluation indicated that a conclusion of non-inferior efficacy and safety may be more appropriate. Results from pooled analyses of CZP trials comparing CZP 200 mg and CZP 400 mg also indicated no significant differences between the two doses, although the PASI 75 responder rate was numerically higher in the CZP 400 mg group based on the pooled analyses. No evidence was presented in the submission against other alternative bDMARDS (IXE, IFX, SEC and GUS). These alternative bDMARDs may be more effective or less costly than CZP.

6.27 The cost analysis presented the costs over a period of one year (52 weeks) based on maintenance treatment only. This is inconsistent with the cost-minimisation analysis approach for bDMARDs for CPP previously accepted by the PBAC, which is conducted over two years, and includes both induction and continuation treatments. The PSCR stated that the approach taken by the submission is appropriate and consistent with the methodology applied to other bDMARDs. The ESC noted that conducting the CMA over 2 years and including both induction and maintenance doses was consistent with the methodology applied to recently listed bDMARDs.

6.28 The submission estimated equi-effective doses for CZP, UST and ADA based on the recommended maintenance doses ('steady state') in the respective PI's. The submission acknowledged the weight based dosing for UST (45 mg for patients weighing $\leq$ 100 kg or 90 mg for patients weighing > 100 kg) at Weeks 0, 4 and then every 12 weeks thereafter and applied an "average mg/dose" for UST (59.38 mg) based on information from the secukinumab March 2015 Public Summary Document (PSD). The PSCR stated that there is no precedence for using the highest dose of other bDMARDs in determining dose equivalency. The ESC noted that the higher doses for other bDMARDs are for patients that require dose escalation and are not the recommended doses.

6.29 The submission considered the below doses to be equi-effective:

CZP 200 mg Q2W

≡ UST 45 mg (or UST 90 mg for patients >100 kg) Q12W;

≡ ADA 40 mg Q2W.

The submission did not consider the loading doses in the calculation of equi-effective doses. Conventionally, the equi-effective doses of bDMARDs, as outlined in the Therapeutic Relativity Sheets also include the respective loading doses. The ESC advised CZP 400 mg should be considered the equi-effective dose for CZP as it was the recommended dose in the draft PI provided with the submission and was supported by the TGA Delegate.

6.30 UST and ADA are currently listed on the PBS under an SPA. As the Sponsor for CZP did not have access to SPA details for UST or ADA, the cost analysis was based on the published prices. The submission reasonably assumed that there would be no additional administration costs for CZP compared to UST.

Drug cost/patient/year: $[redacted] (CZP 400 mg) or $[redacted][5] (CZP 200 mg), costs calculated over Year 1 of treatment (i.e. inclusive of induction and maintenance periods).

6.31 Using the requested dispensed price per maximum quantity (DPMQ) of $1,014.61 per pack of two 200 mg injections, and assuming the CZP 400 mg dosing regimen, the drug cost of CZP was estimated to be $[redacted] per patient per year. Assuming the CZP 200 mg dosing regimen, the drug cost of CZP was estimated to be $[redacted] per patient per year. Eligibility for PBS-subsidised continuation treatment is dependent upon the achievement and maintenance of a PASI 75 response.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. A market share approach was used to estimate the financial implications of the proposed listing. Department of Human Services (DHS) PBS/RPBS data were used to estimate the market size of comparator bDMARDs, however, the projected growth rate of all bDMARDs for CPP appeared to be arbitrary assumptions. The estimated number of CZP prescriptions was based on (assumed) uptake rates and estimated prescription substitution rates of currently listed comparator bDMARDs.

6.33 Despite the assumptions stated by the submission that CZP would predominantly displace UST and ADA, the uptake rates applied for CZP were identical for ADA, UST, SEC, IXE and ETN. The submission assumed that CZP would not displace the use of IFX on the assumption that, as IFX has a different method of administration (IFX is administered as an intravenous infusion rather than as a subcutaneous injection), it is a deliberate choice for doctors and patients. The submission also assumed that ETN

[5] Rounded to 15 prescriptions. Patients who are prescribed the CZP 200 mg Q2W regimen would require 29 injections for treatment up to 52 weeks, which equates to 14.5 prescriptions.

25 mg powder for injection would not be substituted by CZP, due to it having a different presentation (i.e., requiring reconstitution prior to administration rather than as a prefilled syringe ready to be administered), instruction for use and relatively low utilisation per year. This assumption may not be entirely reasonable, however, as the rate of substitution from these drugs are likely to be low, the impact on the financial estimates are likely to be minimal.

6.34 The submission inappropriately only accounted for the use of CZP 200 mg in its base case financial estimates. Based on the CZP 200 mg dose, the requested initial PBS restriction would allow up to 18 weeks of treatment, with the last injection given at Week 16. Script equivalence for initial treatment for comparator bDMARDs was then estimated based on the respective PI recommended doses and maximum PBS quantities for initial treatment. The requested quantity providing 18 weeks of CZP 200 mg treatment is inconsistent with the requested restrictions (stating that patients must receive no more than 16 weeks of treatment under the restriction, with assessment of PASI response after at least 12 weeks of treatment). PASI non-responders after Week 12 therefore may not require a further dose of CZP prior to Week 16, leading to wastage. Furthermore, for patients who are prescribed CZP 400 mg, the requested restriction would only allow up to 12 weeks of treatment, with the last injection given at Week 10. Script equivalence to comparator biologics would hence differ, dependent on whether comparator scripts were displaced by the CZP 200 mg or 400 mg dose.

6.35 The estimated net financial implications for the proposed listing of CZP (based on the CZP 200 mg dose) for CPP over the first 6 years is presented in Table 9.

Table 9: Estimated net financial implications of the proposed CZP listing as presented by the submission, based on published prices.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Biologic scripts displaced by CZP (substitution rate[a] to CZP scripts: initial/continuing)						
ADA (1.2/1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST (2/3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC (1.83/1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE (1.33/2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg (1.5/1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP scripts[b]						
Initial[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS (minus patient copayment)						
CZP net cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Comparators net cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net cost	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Abbreviations: ADA=adalimumab; CZP=certolizumab pegol; ETN=etanercept; IXE=ixekizumab; SEC=secukinumab; UST=ustekinumab

[a] Substitution rates were incorrectly calculated by the submission

[b] Calculated from the number of scripts of the comparator medicine displaced x the substitution rate x uptake rate of CZP

[c] Split between initial and continuing based on the proportional split in the first six years' of ADA PBS listing
Source: constructed during evaluation from the Section 4 workbook accompanying the submission.

The redacted table shows that at Year 6, the estimated number of prescriptions was less than 10,000 and the net cost to the PBS/RPBS would be less than $10 million.

6.36 Although the financial estimates presented by the submission show that the proposed listing of CZP is estimated to save less than $10 million over six years, this is unlikely to be realised given that the cost offsets for displaced bDMARDs were calculated based on published prices.

6.37 It was inappropriate that the submission's base case financial model assumed all patients would be prescribed the CZP 200 mg dose, as it is likely that most patients will be prescribed CZP 400 mg in the PBS setting. Based on the submission's requested DPMQ, the cost of CZP would be almost double the submission's estimates, if most patients were prescribed the CZP 400 mg dose in the PBS setting. This would result in significant cost implications for the government. The Pre-PBAC Response argued the available data from Germany indicated the proportion of patients who will require ongoing use of a 400 mg dose will be approximately 10-15% of patients.

6.38 The ESC considered the financial estimates in the submission unreliable as the CMA for CZP was not appropriate and cost offsets were based on published prices.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of certolizumab pegol (CZP) on a cost minimisation basis with the least costly biological disease-modifying anti-rheumatic drug (bDMARD) for chronic plaque psoriasis (CPP). In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs for CPP could be an alternative therapy to CZP.

7.2 The PBAC considered the equi-effective doses of certolizumab pegol (at a dose of 400 mg every 2 weeks) and alternative bDMARDs could be derived from the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets.

7.3 The PBAC noted that eight alternative bDMARDs were listed on the PBS for the treatment of CPP at the time of consideration. The PBAC considered that while the clinical need for an additional treatment with a mechanism of action the same as several other listed bDMARDs (tumour necrosis factor-alfa inhibitor) was low, the PBAC noted there may be advantages for patients who are either pregnant or intending to become pregnant as it is unlikely to cross the placenta.

7.4 The submission nominated ustekinumab (UST) and adalimumab (ADA) as the primary comparators on the basis these were the most prescribed therapies in practice. The PBAC considered the nominated comparators were appropriate but noted all PBS listed biologic therapies for CPP are alternative therapies and could be substituted by CZP. As described in Section 5.3 above, CZP could only be recommended for listing

with a higher price than alternative therapies if the PBAC is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction in toxicity.

7.5 No evidence was presented in the submission to support a claim that CZP provided a significant improvement in efficacy or reduction in toxicity compared to any of the currently PBS listed bDMARDs for severe CPP. The PBAC noted the results of the direct comparison with etanercept and indirect comparisons with UST and ADA supported a conclusion of non-inferior comparative effectiveness and safety between CZP and these therapies.

7.6 Based on the evidence presented in the submission (for CZP 200 mg) and analyses conducted during evaluation (for CZP 400 mg), the PBAC was satisfied that non-inferiority to UST and ADA was supported for both doses. The PBAC considered that CZP 400 mg was the most likely dosage regimen to be used in practice. The PBAC considered that, given patients could only fail a maximum of 3 biologic agents in a five year period for CPP, clinicians and patients were likely to want to use the higher dose of CZP to ensure the best opportunity of an ongoing response to treatment. Additionally, TNF inhibitors generally required higher doses to treat patients with CPP, especially those who are treatment experienced.

7.7 The PBAC considered that if CZP (at a dose of 400 mg every 2 weeks) was listed on the PBS on the basis of cost-minimisation to the lowest cost alternative bDMARD there was likely to be a small net cost saving as it may substitute for more costly alternatives.

7.8 PBAC considered that it would be appropriate to price CZP 200 mg on the same per mg basis as CZP 400 mg.

7.9 The PBAC considered it would be appropriate to align the listing of CZP with the other written authority bDMARD listings for CPP, and that flow-on changes to the notes in other listings to include CZP in the list of therapies would be required to facilitate the listing.

7.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that certolizumab pegol may be treated as interchangeable on an individual patient basis with adalimumab, etanercept, guselkumab, infliximab, ixekizumab, secukinumab, tildrakizumab and ustekinumab for severe chronic plaque psoriasis.

7.11 The PBAC advised it remained of the view that certolizumab pegol is not suitable for prescribing by nurse practitioners.

7.12 The PBAC noted this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Restriction to be finalised.

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 had no comment.