

6.01 ABATACEPT, 125mg SC injection (auto-injector and pre-filled syringe) and 250mg vial for IV infusion, Orencia[®], Bristol-Myers Squibb.

1 Purpose of Application

- 1.1 Authority Required (in writing) listing of abatacept for treatment of severe active psoriatic arthritis (PsA) in patients meeting certain criteria. This is the first submission of abatacept for PsA to be considered by the PBAC. Abatacept was listed on the PBS for the treatment of rheumatoid arthritis (RA) in 2008; a submission for the treatment of juvenile idiopathic arthritis (JIA) was considered by the PBAC in July 2011 and the decision was deferred.
- 1.2 The basis for the requested listing was a cost-minimisation analysis to the following biologic disease-modifying anti-rheumatic drugs (bDMARDs) currently listed on the PBS: certolizumab pegol, ustekinumab, and secukinumab. While any bDMARD listed on the PBS for PsA could be an appropriate comparator, the submission noted that certolizumab, ustekinumab and secukinumab represented a 'lower-tier' of less expensive alternatives on the PBS. The nomination of certolizumab, ustekinumab and secukinumab as comparators was reasonable, however should the effective prices of any 'higher tier' bDMARDs actually be lower than the requested price of abatacept, they would also be relevant comparators. The cost calculation presented included secukinumab as the only comparator, which was listed on a cost-minimisation basis to certolizumab and ustekinumab.

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

Component	Description
Population	Adults with severe active psoriatic arthritis
Intervention	Abatacept 125mg SC weekly; or Abatacept ~10mg/kg ^a IV at weeks 0, 2, 4, then every 4 weeks.
Comparators	Certolizumab 400mg SC at weeks 0, 2, 4, then either 200mg every 2 weeks or 400mg every 4 weeks; Ustekinumab 45mg SC at weeks 0, 4, then every 12 weeks; Secukinumab 150mg or 300mg ^b SC at weeks 0, 1, 2, 3, 4, then every 4 weeks.
Outcomes	ACR50 and to a lesser extent ACR20 given ACR50 reflects to a greater degree the criteria for current PBS eligibility for continuing treatment. The PBAC has previously considered indirect comparisons of ACR50 and ACR20 of other bDMARDs at a time points consistent with the assessment of response on the PBS.
Clinical claim	In adults with severe active psoriatic arthritis, abatacept is no worse than the nominated comparators (certolizumab, ustekinumab and secukinumab) at treating the disease measured across several outcomes when interpreted collectively (ACR20, ACR50, PASI75, HAQ-DI, Quality of Life), and no worse than the nominated comparators in terms of safety.

ACR20/50 = ≥20% /50% improvement on the American College of Rheumatology Criteria; bDMARD = biologic disease-modifying anti-rheumatic drug; IV=intravenous; SC=subcutaneous; PASI75 = ≥75% reduction in the Psoriasis Area and Severity Index; HAQ-DI = Health Assessment Questionnaire Disability Index; PBS = Pharmaceutical Benefits Scheme

^a <60kg: 500mg, 60-100kg: 750mg, >100kg: 1g

^b 300mg recommended for anti-TNF-α inadequate responders or patients with concomitant moderate to severe plaque psoriasis.

Source: Table 51, p117 of the submission.

2 Requested listing

- 2.1 PBS listing of abatacept was requested for three formulations: i) a 125mg auto-injector for subcutaneous (SC) administration, ii) a 125mg pre-filled syringe for SC administration, and iii) a 250mg vial (powder) for intravenous (IV) infusion (reconstitution with 10ml of water for injection).
- 2.2 An abbreviated form of the requested listing was presented in the submission; the Sponsor requested alignment of the requested restriction with the wording of the other bDMARDs currently listed for severe active PsA. For consistency with the other bDMARDs: the SC and IV formulations would need to be restricted as authority required (in writing) S85 and S100 items respectively.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ABATACEPT, single dose auto-injector (4), 125mg	1	4	NR	\$ [REDACTED]	ORENCIA®, Bristol-Myers-Squibb Australia Pty Ltd
ABATACEPT, single dose pre-filled syringe (4), 125mg	1	4	NR	\$ [REDACTED]	
ABATACEPT, powder for IV infusion (1), 250mg	1	1	NR	\$ [REDACTED]	
PBS indication:	Severe active psoriatic arthritis				
Treatment phase:	Initial treatment – initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)				
Clinical criteria:	Patient must have severe active psoriatic arthritis, AND Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR Patient must have received no PBS-subsidised treatment with a biological agent for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent for this condition, AND Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, AND Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; OR Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months AND Patient must not receive more than 24 weeks of treatment under this restriction.				
Treatment phase:	Continuing treatment				
Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis AND Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition in the current Treatment Cycle AND Patient must demonstrate, at the time of application, an adequate response to treatment with this drug AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.				

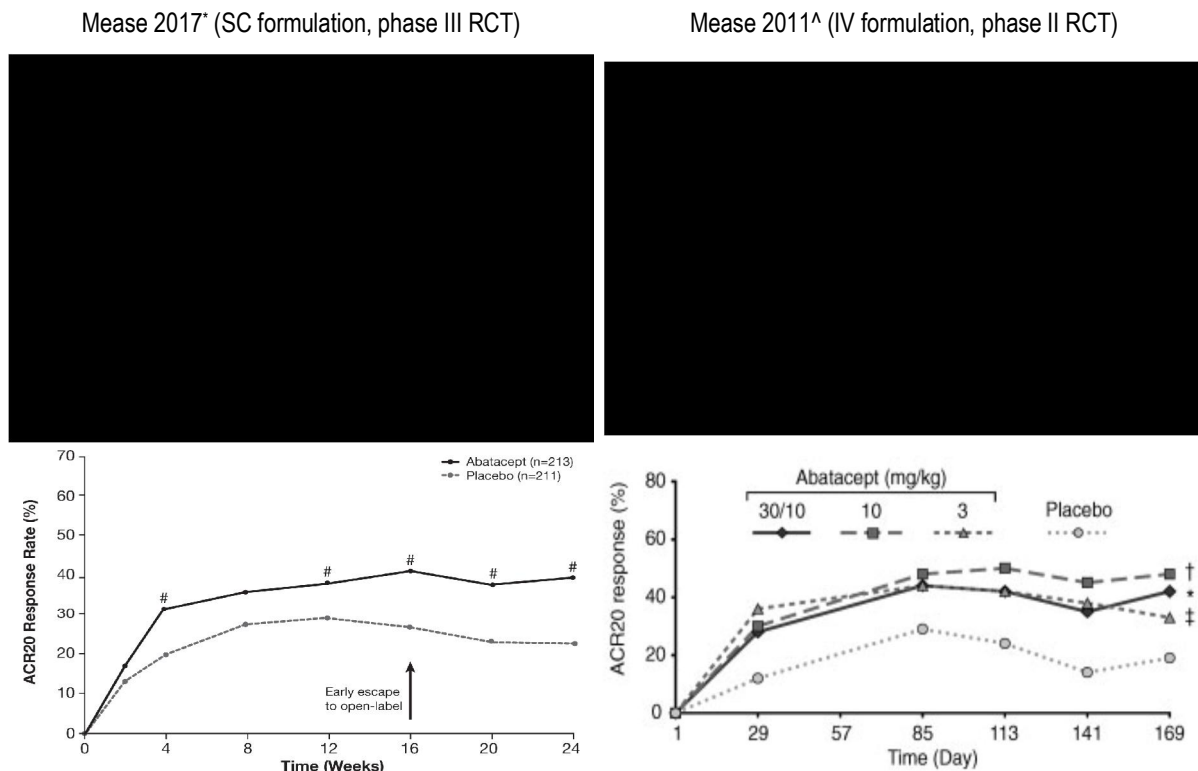
Source: Table 19, p28 of the submission.

- 2.3 No special pricing arrangements were proposed in the submission. Based on the requested quantities and recommended dosing regimens, each pack of the SC formulations would provide for one-month supply of treatment (i.e. 125mg once weekly), whereas the number of vials for IV infusion is dependent on the patient

weight (i.e. <60kg: 2 vials per dose; 60-100kg: 3 vials per dose; >100kg: 4 vials per dose) and whether the patients is initiating or continuing treatment (i.e. administered at Week 0, 2, 4, then every 4 weeks).

- 2.4 The submission did not justify why 24 weeks of initial treatment was requested, or provide a rationale for why abatacept may take longer to work in PsA than RA, for which abatacept is only PBS listed for a maximum of 16 weeks of initial therapy. Figure 1 presents the proportion of patients who achieved a 50% and 20% improvement in the American College of Rheumatology Criteria (ACR50 and ACR20, respectively) with abatacept in Mease 2011 and Mease 2017. A similar proportion of patients had achieved an ACR50 and ACR20 response by Week 16 (Day 85) compared with Week 24 (Day 169). Given the relatively quick time-to-response and relatively flat response rate after Weeks 12-16, the requested restriction may delay patients who do not respond to abatacept from accessing a potentially more effective therapy by up to 8 weeks.
- 2.5 The PBAC noted that in its Pre-Sub-Committee Response (PSCR), the sponsor agreed with the evaluation and accepted the proposed change to 16 weeks of initial treatment duration.

Figure 1: ACR50 and ACR20 response over 24 weeks in the abatacept trials: Mease 2011 and Mease 2017



Abbreviations: ACR20/50 = $\geq 20\%$ / 50% improvement on the American College of Rheumatology Criteria

* early escape patients switched to open-label abatacept at Week 16 were imputed as non-responders at Weeks 20/24.

^ Note the relevant ABA treatment arm is the ABA 10/10 or ABA 10 (~10mg/kg dose for induction and maintenance).

Source: Figure 7.2.5-1, p98 of IM101332 CSR; Figure 7.3.2-2 in IM101158 CSR; Figure 2, Mease et al 2017; Figure 1, Mease et al 2011.

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

3 Background

Registration status

- 3.1 TGA status at time of PBAC advice. The submission was made under TGA/PBAC Parallel Process. Abatacept was approved for registration by the TGA on 10 January 2018 for the treatment of active PsA. Abatacept was TGA registered for RA in 2007 and JIA in 2009.
- 3.2 The evidence to support the IV formulation of abatacept in PsA was limited as it was only evaluated in a Phase 2b dose ranging trial and only 40 patients were treated with the proposed IV dose. The TGA delegate accepted that the IV and SC regimens were therapeutically equivalent based on evidence in RA, comparable pharmacokinetics, comparable predicted exposure-response rates, and comparable observed treatment effect.
- 3.3 A panel of Australian rheumatologists (Sponsor commissioned) considered that the availability of the IV formulation was important to ensure adequate dosing of patients with a high body mass index (BMI).
- 3.4 The PBAC and ESC noted that the TGA evaluation (TGA Round 2 Clinical Evaluation Report p31) reported, based on a population pharmacokinetic analysis, that either the SC or IV formulation would result in 95% of the PsA population achieving therapeutic steady state concentrations. The PBAC and ESC considered that the claim provided in the PSCR, in favour of another weight-based IV dosing option for patients with high Body Mass Index (BMI), to be not relevant as adequate concentrations can be achieved with the SC formulation for patients regardless of body weight.

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

4 Population and disease

- 4.1 PsA is an inflammatory joint disease associated with psoriasis. It is an irreversible, progressive and heterogeneous disease which can involve the peripheral joints (arthritis), axial skeleton (spondylitis), insertion of tendons and ligaments into bone (enthesitis), inflammation of whole digits (dactylitis), skin and nails. Joint damage can lead to marked disability and reduced quality of life.
- 4.2 Abatacept (a "T cell co-stimulation modulator") is a recombinant human monoclonal antibody which modulates a key co-stimulatory signal required for full activation of T

lymphocytes expressing CD28. Activated T lymphocytes contribute to the pathogenesis in a number of autoimmune diseases including PsA.

- 4.3 There are currently seven bDMARDs PBS listed for patients with severe active PsA who have failed to achieve an adequate response to non-biologic DMARDs. ESC considered that the addition of abatacept to the clinical management algorithm will not significantly alter current practice, but will allow for an additional option with a different mechanism of action. It was anticipated by the sponsor that abatacept would predominately be prescribed as 3rd-line therapy after a tumour necrosis factor (TNF) α inhibitor (1st-line) and secukinumab (2nd-line), or as 2nd-line therapy in patients with comorbidities precluding treatment with secukinumab (e.g. patients with inflammatory bowel disease).

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

5 Comparator

- 5.1 The submission nominated certolizumab, ustekinumab and secukinumab as the main comparators. While any bDMARD listed on the PBS for PsA including etanercept, adalimumab, infliximab and golimumab could be an appropriate comparator, the nominated comparators represented the 'lower-tier' of alternatives on the PBS.

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 and welcomed the input from two organisations, 'CreakyJoints Australia' and 'Psoriasis Australia', health Professionals (5), and individuals (11) via the Consumer Comments facility on the PBS website. The comments noted support for the availability of a drug with a new mode of action, for patients who have trialled and failed other bDMARDs and for patients who are intolerant to the currently available bDMARDs. The potential benefits of treatment with abatacept were noted to include the ability to return to work, fewer side effects and quality of life improvement.

Clinical trials

- 6.3 The submission is based on six placebo-controlled trials comparing abatacept or one of the nominated comparators (certolizumab, ustekinumab, secukinumab) to

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Abatacept versus placebo		
Mease 2011	A Phase IIB, Multi-Dose, Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept Versus Placebo in the Treatment of Psoriatic Arthritis Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: Results of a six-month, multicentre, randomized, double-blind, placebo-controlled, phase II trial.	Final Clinical Study Report for Study IM101158 (6-month). November 2009. Arthritis and Rheumatism. 2011; 63(4):939-48.
Mease 2017 (ASTRAEA)	A Phase 3 Randomised Placebo Controlled Study to Evaluate the Efficacy and Safety of Abatacept Subcutaneous Injection in Adults with Active Psoriatic Arthritis. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis.	Final Clinical Study Report for Study IM101-332. August 2016 Annals of the rheumatic diseases. 2017; 76(9):1550-8.
Certolizumab versus placebo		
RAPID-PsA	Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA).	Annals of the Rheumatic Diseases. 2014;73(1):48-55.
Ustekinumab versus placebo		
PSUMMIT 1	McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. 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.	The Lancet. 2013;382(9894):780-9.
PSUMMIT 2	Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. 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 anti-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 the Rheumatic Diseases. 2014;73(6):990-9.
Secukinumab versus placebo		
FUTURE 2	McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet. 2015;386(9999):1137-46.

Source: Tables 21-22, p33 and pp37-37 of the submission.

6.4 The key features of the direct randomised trials are summarised in the table below. Four trials randomised patients to one or more arms of active treatment using dose regimens which are not relevant/approved in the Australian setting; data from these arms were appropriately excluded in the submission.

Table 3: Key features of the included evidence

Trial	N	Design / duration	Relevant comparison	Risk of bias	Patient population	Key outcomes
Abatacept versus placebo						
Mease 2011	82 ^a	Phase 2b, MC, R, BD; 24wks.	ABA 10mg/kg ^b IV wk0, 2, 4, q4w; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50
Mease 2017	424	Phase 3, MC, R, BD for 24wks; EE to OL active at wk16 if 'non-responder' ^c ; OL from 24-52wks.	ABA 125mg SC q1w; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50
Certolizumab versus placebo						
RAPID-PsA	409	Phase 3, MC, R, BD for 24wks; PBO crossover at wk16 if 'non-responder' ^d , or wk24 for responders; dose-blind from 24-48wks; OL from 48-216wks.	CZP 400mg SC wk0, 2, 4, 200mg q2w or 400mg q4w; vs PBO	Low	Active PsA	1°: ACR20 wk12 & ΔmTSS wk24; 2°: ACR50
Ustekinumab versus placebo						
PSUMMIT 1	411 ^a	Phase 3, MC, R, BD for 24wks; PBO crossover or active dose escalation at wk16 if 'non-responder' ^e , or wk24 for PBO responders; OL from 24-108wks.	UST 45mg SC wk0, 4, q12w; vs PBO	Low	Active PsA, (TNF-α naïve)	1°: ACR20 wk24; 2°: ACR50
PSUMMIT 2	207 ^a	Phase 3, MC, R, BD for 24wks; PBO crossover or active dose escalation at wk16 if 'non-responder' ^e , or wk24 for PBO responders; OL from 24-60wks.	UST 45mg SC wk0, 4, q12w; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50
Secukinumab versus placebo						
FUTURE 2	298 ^a	Phase 3, MC, R, BD for 24wks; PBO crossover at wk16 if 'non-responder' ^f , or wk24 for responders; OL from 24-256wks.	SEC 150mg or 300mg wk0, 1, 2, 3, 4, q4w; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50

Abbreviations: EE = early escape; OL=open label; PBO = placebo; R = randomised; BD = double blind; MC = multicentre; mTSS=modified total sharp score; ACR20/50 = ≥20% /50% improvement on the American College of Rheumatology Criteria; PsA= Psoriatic Arthritis

^a excluding patients randomised to arms which were not relevant to the submission.

^b patients received a weight tiered dosing regimen approximated to 10mg/kg: <60kg=500mg, 60-100kg=750mg, >100kg=1g.

^c patients (on ABA or PBO) with <20% improvement in swollen and tender joint count at week 16 from baseline commenced OL ABA

^d patients on PBO with <10% improvement in swollen and tender joint count at week 16 from baseline were re-randomised to CZP 200mg q2w or 400mg q4w after the loading doses; all PBO patients were re-randomised at week 24.

^e patients on PBO or UST 45mg with < 5% improvement in swollen and tender joint count at week 16 from baseline were initiated on UST 45mg and UST 90mg respectively; all PBO patients commenced UST 45mg at week 24.

^f patients on PBO with <20% improvement in swollen and tender joint count at week 16 from baseline were re-randomised to SEC 300mg or 150mg.

Source: compiled during the evaluation from the trial publications

6.5 The overall risk of bias of the included trials was considered low, although there were much higher rates of discontinuation for patients treated with placebo compared with active treatment across the trials. The potential that prescribers and patients could determine the assignment of groups may have impacted on some outcomes, but any bias would likely be comparable across trials.

6.6 All trials had a double-blind phase of 24 weeks, however most required patients who did not meet minimum response criteria after Week 16 in the placebo arm or both placebo and active arms to commence open-label active treatment. The criteria for 'early escape' differed across the trials which were argued to bias against abatacept in the indirect comparisons conducted at Week 24. Given the criteria were easier to fulfil in Mease 2017, and since it was also applied to the active treatment arm, it was

argued that fewer patients on abatacept would have had the opportunity to demonstrate a response by Week 24.

Comparative effectiveness

- 6.7 On the PBS, response to bDMARD therapy for PsA is currently determined by criteria similar to the ACR50 and ACR20 response criteria, assessed at various time points depending on the individual bDMARD (i.e. Week 12-16 for secukinumab, Week 12-18/20 for certolizumab depending on the dose, and ~Week 12-28 for ustekinumab). ACR20 was the primary outcome in all of the included trials, assessed at Week 12 in RAPID-PsA and Week 24 in the other trials. ACR50 and ACR20 at various times were either secondary or exploratory outcomes.
- 6.8 The PBAC has previously considered that: i) joint response (rather than skin response) was the most important outcome in PsA; ii) “ACR50 was the outcome of most interest ... [given] it is more stringent than ACR20 and reflects to a greater degree the criteria for the current PBS eligibility for continuing treatment with a bDMARD”; and iii) it is appropriate to determine the price of the bDMARDs based on the ACR50 outcome alone (see Ustekinumab PSD, November 2014). However, ACR20 has also been used to support non-inferiority in past decisions (see Certolizumab PSD, November 2014; Secukinumab PSD, March 2016).
- 6.9 Non-inferiority margins for ACR50 and ACR20 were nominated based on the PBAC’s consideration of secukinumab (see Secukinumab PSD March 2016). For non-inferiority to be demonstrated, there must not be a statistically significant difference in the indirect comparisons, and the lower bound of the 95% confidence interval (CI) around the relative risk (RR) must exceed 0.29 for ACR50 and 0.46 for ACR20.
- 6.10 The trial results for ACR50 and ACR20 at Week 24 indicated that the biologics were more effective than placebo at producing a response with one key exception. Although numerically higher, the proportion of patients who achieved an ACR50 response on abatacept was not statistically significantly different to placebo in Mease 2017. The failure of this secondary endpoint may in part be due to the high proportion of early escape patients subsequently classified as non-responders (36% on abatacept and 42% on placebo).
- 6.11 The submission presented a series of indirect comparisons for several outcomes including ACR50 and ACR20 at Week 24, summarised in Table 4. No justification was provided in the submission for conducting the indirect comparisons at Week 24, but it may be related to the timing of the primary endpoint (in most trials) or end of the double-blind phase (in all trials).

Table 4: Summary of indirect comparisons for outcomes at 24 weeks

Outcome and indirect comparison	RR (95%CI)	RD (95%CI)
ACR50 (ITT, 24 Weeks)		
ABA (meta-analysis) vs CZP (pooled)	0.94 (0.14, 6.30)	-0.16 (-0.33,0.01)
ABA (meta-analysis) vs UST (meta-analysis)	1.14 (0.17, 7.57)	0 (-0.16,0.16)
ABA (meta-analysis) vs SEC (pooled)	0.65 (0.09, 4.76)	-0.14 (-0.32,0.04)
ACR20 (ITT, 24 Weeks)		
ABA (meta-analysis) vs CZP (pooled)	0.73 (0.48,1.12)	-0.18 (-0.31,-0.05)
ABA (meta-analysis) vs UST (meta-analysis)	0.96 (0.66, 1.39)	-0.02 (-0.13,0.09)
ABA (meta-analysis) vs SEC (pooled)	0.55 (0.31,0.95)	-0.18 (-0.31,-0.05)

Abbreviations: ABA = abatacept; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab;

Source: Tables 48-49, pp110-112 of the submission;

Bolded values reached statistical significance $p < 0.05$; Italics indicates estimates corrected or performed during the evaluation.

- 6.12 For the ITT population at Week 24, non-inferiority could not be concluded between abatacept and any of the comparators for ACR50, or between abatacept and secukinumab for ACR20. The lower 95%CI of the RR estimates of ACR20 for abatacept versus certolizumab (0.48) and ustekinumab (0.66) were higher than the nominated threshold of 0.46.
- 6.13 However, comparisons at Week 24 may not be informative to the PBAC for a number of reasons: i) it is not consistent with the time point when patient response to initial therapy is assessed on the PBS for the nominated comparators, with the exception of ustekinumab; ii) it is not consistent with the time point on which previous PBAC decisions and non-inferiority margins have been based (Week 12 for certolizumab and secukinumab, and Week 24 for ustekinumab; see Secukinumab PSD March 2016); iii) the requested PBS listing of abatacept would permit a maximum of 24 weeks of initial therapy with assessment of response conducted between 12 and 20 weeks given response must be assessed after a minimum of 12 weeks and no later than 4 weeks from the cessation of the treatment course on the PBS; and iv) the requested maximum 24 weeks of initial abatacept therapy may not be supported by the clinical evidence given the relatively flat time-to-response curves after Weeks 12-16 (see Figure 1).
- 6.14 Therefore, indirect comparisons of ACR50 and ACR20 between abatacept (Week 12) and certolizumab (Week 12), ustekinumab (Week 24) and secukinumab (Week 12) were conducted during the evaluation, summarised in Tables 5 and 6. Comparisons in anti-TNF α experienced patients were also presented by the submission given abatacept was most likely to be used as second- or third-line therapy. However, the submission did not test for potential effect under-powering and/or point-estimate imprecision in the subgroup, and the requested restriction does not preclude anti-TNF α naïve patients from receiving treatment.
- 6.15 For the ITT population at Week 12/24, non-inferiority could not be concluded between abatacept and secukinumab for ACR50, or between abatacept and any of the comparators for ACR20. The lower 95%CI of the RR estimates of ACR50 for abatacept versus certolizumab (0.35) and ustekinumab (0.41) were higher than the

nominated threshold of 0.29. These results for ACR50 however were contradicted by the results of indirect comparisons using the RD statistic, which indicated significantly lower proportions of patients attained an ACR50 response with abatacept compared to certolizumab (RD(95%CI): 0.13 (-0.23, -0.03)).

Table 5: ACR50 response at 12 or 24 weeks across the trials, in the ITT and TNF-α experienced populations

Trial	Drug n/N (%)	Placebo n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
ABA (ITT, 12 weeks)					
Mease 2011 (IV)	NR	NR	-	-	
Mease 2017 (SC)	39/213 (18)	17/211 (8)	2.27 (1.33, 3.89)	0.10 (0.04, 0.17)	10 (6,25)
Meta-analysis	-	-	-	-	
ABA (TNF-α experienced, 12 weeks)					
Mease 2011 (IV)	NR	NR	-	-	
Mease 2017 (SC)	21/129 (16)	8/130 (6)	2.65 (1.22, 5.75)	0.10 (0.03, 0.18)	10 (6,25)
Meta-analysis	-	-	-	-	
CZP (ITT, 12 weeks)					
RAPID-PsA 200mg	50/138 (36)	15/136 (11)	3.29 (1.94, 5.56)	0.25 (0.16, 0.35)	4 (3,6)
RAPID-PsA 400mg	44/135 (33)	15/136 (11)	2.96 (1.73, 5.05)	0.22 (0.12, 0.31)	5 (3,8)
Pooled	94/273 (34)	15/136 (11)	3.12 (1.88, 5.17)	0.23 (0.16, 0.31)	4 (3,6)
CZP (TNF-α experienced, 12 weeks)					
RAPID-PsA 200mg	NR	NR	-	-	
RAPID-PsA 400mg	NR	NR	-	-	
Pooled	20/54 (37)	1/36 (3)	13.33 (1.87, 95.00)	0.34 (0.20, 0.48)	3 (2,5)
UST (ITT, 24 weeks)					
PSUMMIT-1 45mg	51/205 (25)	18/206 (9)	2.85 (1.72, 4.70)	0.16 (0.09, 0.23)	6 (4,11)
PSUMMIT-2 45mg	18/103 (18)	7/104 (7)	2.60 (1.13, 5.95)	0.11 (0.02, 0.20)	9 (5,50)
Meta-analysis	69/308 (22)	25/310 (8)	2.78 (1.81, 4.27)	0.14 (0.09, 0.20)	7 (5,11)
UST (TNF-α experienced, 24 weeks)					
PSUMMIT-2 45mg	9/60 (15)	4/62 (6)	2.33 (0.76, 7.15)	0.09 (-0.02, 0.19)	NA
SEC (ITT, 12 weeks)					
FUTURE-2 150mg	32/100 (32)	5/98 (5)	6.27 (2.55, 15.43)	0.27 (0.17, 0.37)	4 (3,6)
FUTURE-2 300mg	30/100 (30)	5/98 (5)	5.88 (2.38, 14.53)	0.25 (0.15, 0.35)	4 (3,7)
Pooled	62/200 (31)	5/98 (5)	6.08 (2.52, 14.63)	0.26 (0.18, 0.34)	4 (3,6)
SEC (TNF-α experienced, 12 weeks)					
FUTURE-2 150mg	NR	NR	-	-	
FUTURE-2 300mg	NR	NR	-	-	
Pooled	NR	NR	-	-	
All - CZP,UST,SEC (ITT)					
Meta-analysis	225/781 (29)	45/544 (8)	3.19 (2.35, 4.33)	0.19 (0.13, 0.26)	5 (4,8)
All - CZP,UST (TNF-α experienced)					
Meta-analysis	29/114 (25)	5/98 (5)	4.72 (0.76, 29.20)	0.21 (-0.04, 0.46)	NA
Indirect comparisons, ITT					
ABA (Mease 2017) vs CZP (pooled)			0.73 (0.35, 1.52)	-0.13 (-0.23,-0.03)	NA
ABA (Mease 2017) vs UST (meta-analysis)			0.82 (0.41, 1.62)	-0.04 (-0.13,0.05)	NA
ABA (Mease 2017) vs SEC (pooled)			0.37 (0.13, 1.05)	-0.16 (-0.26,-0.06)	NA
ABA (Mease 2017) vs All (meta-analysis)			0.71 (0.38, 1.32)	-0.09 (-0.18, 0.00)	NA
Indirect comparisons, TNF-α experienced					
ABA (Mease 2017) vs CZP (pooled)			0.20 (0.02, 1.64)	-0.24 (-0.40,-0.08)	NA
ABA (Mease 2017) vs UST (PSUMMIT 2)			1.14 (0.29, 4.44)	0.01 (-0.12, 0.14)	NA
ABA (Mease 2017) vs SEC			-	-	
ABA (Mease 2017) vs All (meta-analysis)			0.56 (0.08, 4.08)	-0.11 (-0.37,0.15)	NA

Abbreviations: ABA = abatacept; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; TNFα = tumour necrosis factor alpha; NR = not reported

Source: constructed during the evaluation based on trial publications. ABA results from p174 of "Round 2 Clinical Evaluation Report – abatacept"; CZP results from Figures 2 and 3, Mease et al 2014; SEC results from Figure 2, McInnes et al 2015;

Bolded values reached statistical significance p<0.05; Italics indicates estimates corrected or performed during the evaluation.

Table 6: ACR20 response at 12 or 24 weeks across the trials, in the ITT and TNF-α experienced populations

Trial	Drug n/N (%)	Placebo n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
ABA (ITT, 12 weeks)					
Mease 2011 (IV)	19/40 (48)	12/42 (29)	1.66 (0.93, 2.97)	0.19 (-0.02, 0.40)	NA
Mease 2017 (SC)	81/213 (38)	61/211 (29)	1.32 (1.00, 1.73)	0.09 (0.00, 0.18)	NA
Meta-analysis	100/253 (40)	73/253 (29)	1.37 (1.07, 1.76)	0.11 (0.02, 0.19)	9 (5,50)
ABA (TNF-α experienced, 12 weeks)					
Mease 2011 (IV)	NR	NR	-	-	NA
Mease 2017 (SC)	47/129 (36)	37/130 (28)	1.28 (0.90, 1.83)	0.08 (-0.03, 0.19)	NA
Meta-analysis	-	-	-	-	-
CZP (ITT, 12 weeks)					
RAPID-PsA 200mg	80/138 (58)	33/136 (24)	2.39 (1.72, 3.32)	0.34 (0.23, 0.45)	3 (2,4)
RAPID-PsA 400mg	70/135 (52)	33/136 (24)	2.14 (1.52, 3.00)	0.28 (0.16, 0.39)	4 (3,6)
Pooled	150/273 (55)	33/136 (24)	2.26 (1.65, 3.11)	0.31 (0.21, 0.40)	3 (3,5)
CZP (TNF-α experienced, 12 weeks)					
RAPID-PsA 200mg	14/31 (45)	4/26 (15)	2.94 (1.10, 7.83)	0.30 (0.07, 0.52)	3 (0,14)
RAPID-PsA 400mg	15/23 (65)	4/26 (15)	4.24 (1.64, 10.96)	0.50 (0.26, 0.74)	2 (1,4)
Pooled	29/54 (54)	4/26 (15)	3.49 (1.37, 8.89)	0.38 (0.19, 0.58)	3 (2,5)
UST (ITT, 24 weeks)					
PSUMMIT-1 45mg	87/205 (42)	47/206 (23)	1.86 (1.38, 2.50)	0.20 (0.11, 0.28)	4 (4,9)
PSUMMIT-2 45mg	45/103 (44)	21/104 (20)	2.16 (1.39, 3.36)	0.23 (0.11, 0.36)	4 (3,9)
Meta-analysis	132/308(43)	68/310 (22)	1.95 (1.52, 2.50)	0.21 (0.14, 0.28)	5 (4,7)
UST (TNF-α experienced, 24 weeks)					
PSUMMIT-2 45mg	22/60 (37)	9/62 (15)	2.53 (1.27, 5.03)	0.22 (0.07, 0.37)	5 (3,14)
SEC (ITT, 12 weeks)					
FUTURE-2 150mg	56/100 (56)	25/98 (26)	2.20 (1.50, 3.21)	0.30 (0.17, 0.43)	3 (2,6)
FUTURE-2 300mg	57/100 (57)	25/98 (26)	2.23 (1.53, 3.26)	0.31 (0.19, 0.44)	3 (2,5)
Pooled	113/200 (57)	25/98 (26)	2.21 (1.55, 3.17)	0.31 (0.20, 0.42)	3 (2,5)
SEC (TNF-α experienced, 12 weeks)					
FUTURE-2 150mg	NR	NR	-	-	-
FUTURE-2 300mg	NR	NR	-	-	-
Pooled	NR	NR	-	-	-
All - CZP,UST,SEC (ITT)					
Meta-analysis	395/781 (51)	126/544 (23)	2.10 (1.77, 2.49)	0.26 (0.20, 0.32)	4 (3,5)
All - CZP,UST (TNF-α experienced)					
Meta-analysis	51/114 (45)	13/88 (15)	2.83 (1.63, 4.93)	0.29 (0.13, 0.45)	3 (2,8)
Indirect comparisons, ITT					
ABA (meta-analysis) vs CZP (pooled)			0.61 (0.41, 0.91)	-0.20 (-0.33,-0.07)	NA
ABA (meta-analysis) vs UST (meta-analysis)			0.70 (0.49, 1.00)	-0.10 (-0.21,0.01)	NA
ABA (meta-analysis) vs SEC (pooled)			0.62 (0.40, 0.96)	-0.20 (-0.34,-0.06)	NA
ABA (meta-analysis) v All (meta-analysis)			0.65 (0.48, 0.88)	-0.15 (-0.25,-0.05)	NA
Indirect comparisons, TNF-α experienced					
ABA (Mease 2017) vs CZP (pooled)			0.37 (0.14, 1.00)	-0.30 (-0.52,-0.08)	NA
ABA (Mease 2017) vs UST (PSUMMIT 2)			0.51 (0.23, 1.10)	-0.14 (-0.33, 0.05)	NA
ABA (Mease 2017) vs SEC			-	-	-
ABA (Mease 2017) v All (meta-analysis)			0.45 (0.23, 0.87)	-0.21 (-0.40,-0.02)	NA

Abbreviations: ABA = abatacept; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; TNFα = tumour necrosis factor alpha; NR = not reported

Source: constructed during the evaluation based on trial publications. ABA results from p27 "IM101158 CSR" (i.e. M-2011) and p152 of "Round 2 Clinical Evaluation Report – abatacept"; CZP results from Figures 2 and 3, Mease et al 2014 and Table 10, p 31 of "EMA/CHMP/601513/2013" reference; SEC results from Figure 2, McInnes et al 2015;

Bolded values reached statistical significance p<0.05; Italics indicates estimates corrected or performed during the evaluation.

- 6.16 Given several sources of heterogeneity across the trials, the findings of the indirect comparisons should be interpreted with caution; however, the PBAC and ESC noted the biases are unlikely to be significant in this case, because:
- Despite differences in early escape rules (at Week 16), those differences are largely not relevant to the indirect comparisons at Week 12/24 and may actually bias against ustekinumab;
 - Despite a higher proportion of patients who had trialled prior anti-TNF α therapy in the abatacept trials (~56% pooled) compared to comparators (certolizumab: ~20% pooled, ustekinumab: ~20% pooled, secukinumab: 35% pooled), the overall findings were relatively comparable in the anti-TNF α experienced subgroup.
 - Despite some variation in placebo response rates across trials and a higher rate in the abatacept trials for ACR20, the differences were not substantial: 5% to 11% for ACR50 (ITT) and 22% to 29% for ACR20 (ITT). They were also relatively more comparable than the older trials of the other 'higher-tier' bDMARDs (etanercept, adalimumab, infliximab, golimumab). The PBAC had previously considered that differences in the placebo response rates between all of these trials "were reasonably offset by the use of the Bucher method to adjust the indirect comparison for event rate differences in the common reference" (see Secukinumab PSD, March 2016).

Comparative harms

- 6.17 The submission presented an informal comparison of limited available safety data for abatacept and the nominated comparators. The percentage of adverse events and serious adverse events on active treatment ranged from 48% to 77.5% and 0% to 9.6%, respectively; infection ranged from 22.9% to 43.5%. No deaths were reported for abatacept or secukinumab (not reported by ustekinumab trials); 2 deaths were reported for certolizumab due to myocardial infarction and unknown cause.
- 6.18 The exchangeability of the trials in terms of safety outcomes was unclear given differences in the time points and handling of 'early escape' patients across the trials. For example, safety data in Mease 2017 was reported for up to 56 days after the last dose in the double-blind phase or first-dose in the open-label phase (whichever came first); FUTURE-2 was based on the first 16 weeks before early escape; whereas RAPID-PsA and the PSUMMIT trials were based on 24 weeks without adjustment for exposure. Placebo event rates for any AEs ranged from 53.1% to 71.4% across the trials.
- 6.19 In the 13th Periodic Benefit-Risk Evaluation Report (PBRER) (22nd Dec 2015), the important identified risks for abatacept were infections and infestations including tuberculous, and infusion (IV formulation) or injection (SC formulation) related reactions.

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

Benefits/harms

6.20 Given that the submission provided no statistical comparisons of safety outcomes, a benefits and harms summary cannot be provided. Summaries of benefits are provided in the 'Comparative effectiveness' section above.

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

Clinical claim

6.21 The submission described abatacept as non-inferior in terms of effectiveness and non-inferior in terms of safety compared with certolizumab, ustekinumab and secukinumab. The basis for this claim was unclear. The submission acknowledged abatacept to be numerically worse than the nominated comparators in terms of key patient relevant outcomes ACR50 and ACR20, as well as PASI75. However, the submission appeared to argue that the trial results were biased against abatacept and given, the results for HAQ-DI, SF-36 PCS and SF-36 MCS were not statistically significantly different in the indirect comparisons, on balance non-inferiority was still supported. Based on the evidence, abatacept appeared to be inferior to certolizumab, ustekinumab and secukinumab for effectiveness:

- the results of the indirect comparisons (at either the Week 12/24 or Week 24 only) showed that abatacept was numerically and statistically significantly inferior to all of the nominated comparators in terms of the patient relevant outcomes ACR50 and ACR20 (ITT population);
- when the non-inferiority margins were applied to the RR statistics (calculated during the evaluation) at Week 12/24 (ITT population), non-inferiority could not be concluded between abatacept and secukinumab for ACR50 or any of the comparators (certolizumab, ustekinumab and secukinumab) for ACR20;
- when the non-inferiority margins were applied to the RR statistics (calculated during the evaluation) at Week 24 (ITT population), non-inferiority could not be concluded between abatacept and any of the comparators (certolizumab, ustekinumab and secukinumab) for ACR50 or secukinumab for ACR20;
- the proportion of patients who achieved an ACR50 response at Week 24 (key secondary outcome) on abatacept was not statistically significantly different to placebo in the phase 3 abatacept trial Mease 2017 (ITT population).
- abatacept was statistically significantly inferior (depending on statistic used) to all of the nominated comparators (certolizumab, ustekinumab and secukinumab) in terms of PASI75 at 24 weeks (psoriasis >3% BSA); and
- Statistical non-significance of underpowered secondary outcomes (HAQ-DI and SF-36) cannot be interpreted as evidence of non-inferiority.

6.22 While not robustly demonstrated given the lack of statistical comparison, a clinical claim of non-inferior safety may be reasonable, and consistent with that previously

accepted by the PBAC for comparisons versus infliximab, etanercept and adalimumab in either RA or JIA.

- 6.23 The PBAC agreed with the ESC that based on the evidence provided, the submission did not demonstrate non-inferiority between abatacept and the nominated comparators (certolizumab, ustekinumab, secukinumab).

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

Economic analysis

- 6.24 A cost-minimisation analysis against certolizumab, ustekinumab and secukinumab was presented.
- 6.25 The equi-effective doses were estimated based on the indirect comparisons of ACR50 and ACR20 presented above, summarised in Table 7. The PBAC has previously accepted the nominated doses of certolizumab, ustekinumab and secukinumab were equi-effective. The PBAC considered, given that non-inferiority between abatacept and the nominated comparators was not adequately supported by the evidence presented in the submission, that the proposed equi-effective doses of abatacept and the nominated comparators were also not be supported.

Table 7: proposed equi-effective doses of ABA, CZP, UST and SEC for severe active psoriatic arthritis

Drug	Dose regimen
ABA	IV: Weight-based dose (<60kg: 500mg; 60-100kg: 750mg; >100kg: 1g) at weeks 0, 2, 4 then every four weeks SC: 125mg every week
CZP	400mg at weeks 0, 2, 4 then either: i) 200mg every two weeks; or ii) 400mg every four weeks
UST	45mg at weeks 0, 4 then every 12 weeks
SEC	Either* 150mg or 300mg# at weeks 0, 1, 2, 3, 4 then every four weeks

Abbreviations: ABA = abatacept; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab;

* alternative dosing considered equivalent.

300mg dose is recommended for patients who are anti-TNF- α inadequate responders or patients with concomitant moderate to severe plaque psoriasis.

Source: Table 51, p117 of the submission

- 6.26 The cost-minimisation analysis was based on the following assumptions:
- Total costs were calculated over a 2-year treatment period (without discounting and despite different initiation periods);
 - The analysis was performed on the DPMQ;
 - Secukinumab was the only cost-comparator included in the analysis;
 - The proportion of patients treated with secukinumab 150mg and 300mg dosing regimens was 50:50 (based on a conservative interpretation of PBS utilisation statistics);
 - The proportion of patients across the weight based dosing categories for the IV formulation of abatacept was derived from a normal distribution with a mean weight of 85kg (SD=17.9).
 - An additional administration cost was applicable to the IV formulation of abatacept (\$71.70/30-minute infusion).

- 6.27 Aside from the two-year time horizon (which has previously been accepted by the PBAC), there were several issues with the assumptions used for the cost-minimisation analysis: i) a cost-minimisation analysis should be conducted on AEMP and not DPMQ; ii) despite different published prices, the PBAC previously recommended both secukinumab 150mg and 300mg regimens at the same price; and iii) abatacept (SC formulation) is associated with an additional 75 SC injections compared with secukinumab over 2 years, a proportion of which would likely incur additional expense due to the need for medical assistance. The PBAC has previously accepted that up to 10% of patients will require assistance with SC administration (see Golimumab PSD, March 2010).
- 6.28 The PBAC agreed with the ESC that a cost minimisation analysis versus the 'lower tier' biologic comparators was not appropriate, as the evidence presented in the submission did not support the conclusion of non-inferiority between abatacept and the nominated comparators.

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

Drug cost/patient/year

- 6.29 \$ [REDACTED] per year for the SC formulation; for the IV formulation, \$ [REDACTED] (\$ [REDACTED] \$1,003.80 administration cost) in the first year and \$ [REDACTED] (\$ [REDACTED] drug cost + \$932.10 administration cost) in the second year and beyond.

Estimated PBS usage & financial implications

- 6.30 This submission was not considered by DUSC. The submission used a market share approach to estimate the financial implications of listing abatacept on the PBS for PsA. Table 8 below summarises the uptake and financial implications of listing abatacept on the PBS for PsA and consists of the following key assumptions made by the submission:
- abatacept would only substitute for the 'lower-tier' bDMARDs (certolizumab, ustekinumab, secukinumab);
 - the requested listing would not increase the current growth in the 'lower tier' bDMARD market beyond the current market growth rate;
 - substitution would be uniform across the comparators (based on the script relativities), with abatacept capturing [REDACTED] to [REDACTED] % of the market over the first 6 years; and
 - the reductions in costs for certolizumab, ustekinumab, secukinumab were estimated based on the average published DPMQs (averaged by PBS services for PsA).

Table 8: Estimated net financial implications of the proposed abatacept listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine						
'Lower tier' bDMARD scripts						
CZP scripts						
UST scripts						
SEC scripts						
Market share (scripts)	%	%	%	%	%	%
Scripts displaced by ABA						
ABA scripts						
SC formulation (4x125mg)						
IV formulation(1x250mg)						
ABA cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
ABA patient co-payment	\$	\$	\$	\$	\$	\$
Net PBS/RPBS cost	\$	\$	\$	\$	\$	\$
Estimation of changes in use and financial impact of other medicines						
CZP,UST,SEC scripts						
CZP scripts						
UST scripts						
SEC scripts						
CZP,UST,SEC cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
CZP cost	-\$	-\$	-\$	-\$	-\$	-\$
UST cost	-\$	-\$	-\$	-\$	-\$	-\$
SEC cost	-\$	-\$	-\$	-\$	-\$	-\$
CZP,UST,SEC patient co-payment	-\$	-\$	-\$	-\$	-\$	-\$
CZP,UST,SEC net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Estimated financial implications for the health budget						
Administration of ABA IV infusion	\$	\$	\$	\$	\$	\$
Net cost to health budget	-\$	-\$	-\$	-\$	-\$	-\$

Abbreviations: ABA = abatacept; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; SC=subcutaneous; IV=intravenous

Source: Tables 58 to 65, pp126-132 of the submission.

6.31 The PBAC considered the predicted use and financial impacts of the proposed listing are not reliable for the following reasons:

- the estimated number of abatacept prescriptions/year was poorly justified because the estimated rate of growth in the 'lower-tier' bDMARDs (~█% in Year 1 to █% in Year 6) and relatively low uptake rates were poorly supported in the submission;
- the submission did not account for additional costs associated with SC administration with abatacept despite requiring much more frequent dosing compared to the nominated comparators; and
- the estimated net financial saving of less than \$10 million over the first 6 years was driven by the reduction in costs associated with the comparators, which was an artefact of using published DPMQs (rather than effective prices) and the assumed script relativities.

- 6.32 The PBAC agreed with the ESC that the expected net cost to the government should be zero given the cost-minimisation analysis presented; or close to zero (depending on the cost of initial treatment, cost of continuing treatment and response rates, across the various bDMARDs).

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend abatacept for the treatment of adult patients with severe active psoriatic arthritis (PsA) due to the low clinical need given the clinical evidence did not support the claim of non-inferior efficacy to the nominated comparators (certolizumab, ustekinumab and secukinumab).
- 7.2 The PBAC accepted that abatacept provides an alternative mode of action to the currently PBS listed bDMARDs and that the drug would most likely be prescribed as a third line agent after a tumour necrosis factor alfa inhibitor (TNF α inhibitor) and secukinumab; or as second-line therapy in patients with comorbidities precluding therapy with sekukinumab. However, due to abatacept being the eighth bDMARD for PsA and the clinical evidence not supporting non-inferiority between abatacept and the nominated comparators, the PBAC concluded that the clinical need to support the listing of the medicine on the PBS for PsA was not adequately justified. The PBAC also did not accept the sponsor's claim that abatacept fulfils a clinical need by providing another weight-based IV dosing option for patients with a high body mass index (BMI).
- 7.3 The PBAC noted the submission nominated the 'lower-tier' of less expensive alternatives bDMARDs (certolizumab, ustekinumab and secukinumab) as the comparators and considered this reasonable. The PBAC also noted that if treatment with abatacept is substantially more costly than any of the bDMARDs currently listed for PsA, the PBAC could only recommend listing of abatacept if it is satisfied that abatacept provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies (National Health Act 1953, Section 101(3B)).
- 7.4 The PBAC noted that the submission presented six randomised clinical trials, comparing abatacept or the nominated comparators versus placebo (two abatacept trials, one certolizumab trial, two ustekinumab trials and one secukinumab trial). The PBAC considered the risk of bias of these clinical trials to be low. The PBAC noted there were some differences across the trials, including differences in the criteria used for switching to open-label therapy.
- 7.5 The PBAC recalled it has previously considered that in PsA the most important outcomes are joint response, rather than skin response, and specifically ACR50 was the outcome of most interest, although ACR20 has also been used to support non-inferiority.

- 7.6 The PBAC considered the clinical claim of non-inferiority of abatacept to the nominated comparators to not be adequately supported for the outcomes of ACR50 or ACR20. Further, the Committee noted based on the indirect comparisons that abatacept was numerically and statistically significantly inferior to all of the nominated comparators for ACR50 and ACR20 (ITT population, relative risk statistic). In addition to being inferior in terms of the joint outcomes, the PBAC noted abatacept was statistically significantly inferior (depending on statistic used) to the nominated comparators in terms of skin response (PASI75 at 24 weeks; psoriasis >3% BSA).
- 7.7 In the pre-PBAC response, the sponsor acknowledged that there were trends in the indirect comparisons that make the claim of non-inferiority with the nominated comparators difficult to interpret, and noted heterogeneity between the clinical trial patient populations and differences in clinical trial design which may bias against abatacept (for example, the more stringent early escape rule used in the abatacept trials versus some of the comparator trials). The sponsor also claimed that for patient-relevant disability and quality of life endpoints (SF-36, HAQ-DI) abatacept demonstrates non-inferiority versus comparators within the standard unadjusted indirect comparison provided. The PBAC considered that statistical non-significance of underpowered secondary outcomes such as HAQ-DI and SF-36 cannot be interpreted as evidence of non-inferiority.
- 7.8 Although the safety comparisons between abatacept and the nominated comparators were limited, the PBAC considered a claim of non-inferior safety may be reasonable, noting non-inferiority has previously been accepted for comparisons versus infliximab, etanercept and adalimumab in rheumatoid arthritis and juvenile idiopathic arthritis.
- 7.9 As non-inferiority for efficacy was not demonstrated between abatacept and the nominated comparators, the PBAC considered that the cost minimisation analysis conducted was not appropriate.
- 7.10 The PBAC considered the predicted use and financial impacts of the proposed listing were not reliable due to poorly justified uptake estimates and not accounting for administration costs due to increased frequency of dosing. The PBAC considered based on the clinical evidence that the uptake of abatacept for the treatment of PsA is likely to be low.
- 7.11 The PBAC noted that in its Pre-PBAC response, the sponsor indicated a willingness to list abatacept for the treatment of PsA at the same price for which it is already listed for the treatment of rheumatoid arthritis, should this lower price resolve residual uncertainties. The PBAC advised that the proposed lower price did not resolve the issues regarding the likely inferior efficacy. The PBAC suggested, based on the inferior efficacy versus alternative bDMARDs, that a comparison versus conventional DMARDs, such as leflunomide, may be informative in any resubmission.

7.12 The PBAC considered that any resubmission must be a major submission and should address the clinical issues as raised above.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.