

7.10 USTEKINUMAB

45 mg/0.5 mL injection, 1 x 0.5 mL vial Stelara[®], Janssen-Cilag Pty Ltd

1 Purpose of Application

1.1 The minor re-submission sought to address the issues raised in the ustekinumab public summary documents from the November 2014 meeting. Namely, the minor re-submission sought to address the following issues:

- TGA-approved dosing for psoriatic arthritis (PsA);
- Clinical need for ustekinumab's alternative mechanism of action;
- Whether the inclusion of rheumatologist prescribing rights to the existing ustekinumab psoriasis restriction would resolve the issue of ustekinumab access for PsA patients;
- Including the additional comparator of certolizumab; and
- Amended price.

2 Requested listing

2.1 The minor re-submission requested the same PBS listing for PsA as that proposed in the November 2014 major submission. The requested restriction is similar in content to the current PBS listings for adalimumab, etanercept, golimumab, infliximab and certolizumab for PsA (except for the proposed duration of initial treatment).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
<u>Initial therapy</u>				
USTEKINUMAB Injections 45mg/0.5ml, 1x0.5ml vial	1	2	Public: \$ [REDACTED] #. Effective: *	Stelara® Janssen-Cilag
<u>Continuing therapy</u>				
USTEKINUMAB Injections 45mg/0.5ml, 1x0.5ml vial	1	1	Public: \$ [REDACTED] 1. Effective: ²	Stelara® Janssen-Cilag

Authority required³

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

¹ This is the same price as in the November 2014 major submission. The minor submission has not updated this price to take consideration of the increase in dispensing fee in 2015, as reflected in the current PBS price of \$ [REDACTED] for ustekinumab for psoriasis.

² Effective price to be determined based on cost-minimisation of ustekinumab 45 mg to certolizumab 200mg. If recommended, the PBS listing for psoriatic arthritis is contingent on a special pricing arrangement being granted, whereby the ustekinumab published price is the same for both the psoriasis and psoriatic arthritis restrictions.

³ The requested restriction is similar to the current PBS listings for adalimumab, etanercept, golimumab, infliximab and certolizumab for PsA (except for the proposed duration of initial treatment). The wording of the requested restriction has not been shown here due to its length.

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

3 Background

- 3.1 Ustekinumab is TGA registered for:
- the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy; and
 - treatment, alone or in combination with methotrexate, of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate. The PsA indication was approved by TGA post the November 2014 PBAC meeting, on 9 February 2015.
- 3.2 The TGA approved dose of ustekinumab for PsA is 45 mg sub-cutaneous injection, administered at Weeks 0 and 4 and then every 12 weeks thereafter. Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.
- 3.3 In November 2014, the PBAC rejected a major submission for ustekinumab for PsA as ustekinumab was considered inferior to adalimumab (the nominated comparator), particularly in terms of joint response. The PBAC also questioned the clinical need for ustekinumab, despite its different mechanism of action to the tumour necrosis factor- α (TNF α) inhibitor agents currently PBS listed for the treatment of PsA (see November 2014 PBAC meeting public summary document – ustekinumab for further details). At the same meeting, the PBAC also considered a submission for certolizumab for PsA, which was recommended on a cost-minimisation basis versus adalimumab. The recommended dose of certolizumab was 400mg (two injections of 200 mg each) delivered at Weeks 0, 2 and 4, followed by either 200 mg every 2 weeks or 400 mg every 4 weeks.
- 3.4 The following table provides a summary of the key differences between the previous major submission and this minor re-submission for ustekinumab.

Key differences between the November 2014 major submission and this minor re-submission

	November 2014 major submission	Current minor re-submission
TGA approval	Submission was lodged under the TGA/PBAC parallel process	Ustekinumab was listed on the ARTG on 9 February 2015 for the treatment of PsA
Ustekinumab dose	patients with body weight ≤100kg: 45mg patients with body weight >100kg: 45mg or 90mg	45mg
Clinical need	Discussion with the PBAC Chair and the PEB suggested that additional clarification of the clinical need of ustekinumab in PsA would be helpful.	Rheumatologists have identified several different PsA patient groups who would benefit from ustekinumab being listed on the PBS.
	The PBAC Chair requested to understand the prescribing barriers for rheumatologists and whether broadening the psoriasis listing or an additional PsA restriction for ustekinumab was required.	Feedback from a dermatologist KOL, Dr [REDACTED]: An expansion of the ustekinumab psoriasis PBS listing would not enable rheumatologists to access ustekinumab.
Main comparator	Adalimumab	Adalimumab, Additional comparator: certolizumab (PBS listed on 1 April 2015)
Requested price (DPMQ)	Special Pricing Arrangement: Initial therapy \$ [REDACTED] based on a [REDACTED] weight price based upon PASI75 and ACR50 results for the pooled 45 mg and 90 mg results. Continuing therapy for patients satisfying eligibility criteria \$ [REDACTED], a [REDACTED]% price reduction on maintenance adalimumab therapy	Weighted price for both the initiation and continuation phase, based on a cost-minimisation consistent with a clinical claim that in terms of ACR50 ustekinumab 45 mg is non-inferior to certolizumab 200 mg.
Clinical evidence	An indirect comparison against comparators using placebo as a common reference, nominating ACR50 as the primary outcome.	
Clinical claim v. adalimumab	Ustekinumab is therapeutically inferior in terms of ACR50 and similar in terms of safety.	
Clinical claim: v. certolizumab	n/a	Ustekinumab is therapeutically non-inferior to certolizumab pegol in terms of ACR50 and non-inferior in terms of safety.
Economic evaluation	Presented a two part economic evaluation based on the results of the indirect comparisons between ustekinumab and adalimumab: 1) a modelled economic analysis for the initiation period to determine a cost for ustekinumab that would give a similar cost per responder compared to adalimumab and 2) a cost minimisation analysis for continuing therapy between ustekinumab and adalimumab.	No economic comparison provided. The effective price of ustekinumab is to be determined based on cost-minimisation of ustekinumab 45 mg to certolizumab 200 mg. Whilst a cost-minimised price of ustekinumab could be calculated from information on the price of certolizumab, the price is not presented in this submission, as it is currently only referenced confidentially.
PBAC decision	Reject	-

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

4 Clinical place for the proposed therapy

- 4.1 The minor re-submission positioned ustekinumab as an alternative bDMARD for PsA patients who have failed therapy with standard DMARDs (p5 of the minor re-submission).

- 4.2 Ustekinumab is an inhibitor of interleukin-12 (IL-12) and IL-23; it belongs to a different therapeutic class and has a different mechanism of action compared with the PBS listed biological TNF α inhibitor therapies. The minor re-submission stated that ustekinumab is believed to interrupt signalling and cytokine cascades that are central to the pathology of PsA and other inflammatory disorders.
- 4.3 The submission asserted that rheumatologists requested the Sponsor to seek PBS reimbursement for ustekinumab for patients with PsA for whom TNF α inhibitor therapies are not suitable. These patients are considered unsuitable due to lack of eligibility, tolerance or response to TNF α inhibitor therapy. However, the restriction proposed by the sponsor does not limit treatment to this patient group. Instead the proposed restriction positions ustekinumab as an alternative to the TNF α inhibitors. The pre-PBAC response clarified that the requested restriction positions ustekinumab as a first and subsequent line therapy for patients with PsA for whom TNF α inhibitors are unsuitable. However, the pre-PBAC response claimed that the majority of ustekinumab use in PsA is expected to follow prior TNF α inhibitor therapy.
- 4.4 The minor re-submission claimed that a small number of PsA patients cannot access first line TNF α inhibitor therapy due to co-morbidities such as moderate to severe heart failure. TNF α inhibitor therapy is also contraindicated in patients with demyelinating disorders, including multiple sclerosis, optic neuritis and peripheral demyelinating disorders, including Guillain-Barre syndrome. In comparison, there are no contraindications contained in the ustekinumab PI that would preclude its use as a treatment for these patients.
- 4.5 The minor re-submission claimed that rheumatologists have identified several different PsA patient groups who would benefit from ustekinumab being listed on the PBS:
- Patients with injection phobia: The re-submission asserted that PsA patients must currently receive either fortnightly or monthly subcutaneous injections or intravenous infusions every eight weeks, and thus ustekinumab's 12 week treatment regime would be of benefit to those patients with injection phobia;
 - Patients presenting with predominantly psoriatic symptoms;
 - Patients developing paradoxical reactions (considered to be a class effect of TNF α inhibitor therapies);
 - Patients with a prior history of malignancy including skin malignancy: The minor submission stated that rheumatologists advised that for patients with a previous history of malignancy, ustekinumab would be used in preference to TNF α inhibitors, if it was listed on the PBS, due to its tolerability and safety profile;
 - Patients needing a methotrexate free regimen: The minor submission stated ustekinumab is usually administered as a monotherapy and therefore it would be the bDMARD of choice for patients such as pregnant women who cannot receive methotrexate.
 - Non-responders to TNF α inhibitor therapy.
- 4.6 An additional issue discussed at the post-PBAC meeting was the PBAC Chair's request that the Sponsor clarify the prescribing barriers for rheumatologists and identify whether broadening the psoriasis listing of ustekinumab on the PBS, instead of including an additional PsA listing, would be sufficient to improve access. Feedback from a dermatologist, Dr [REDACTED], indicated that rheumatologists would not be able to prescribe ustekinumab for patients with PsA (who present with

predominant skin disease) as the PBS listing for psoriasis requires documented failures of prior therapies that are restricted to dermatologist use.

- 4.7 Feedback from the Sponsor’s Rheumatology key opinion leaders also considered the expansion of the existing ustekinumab PBS listing in psoriasis to be insufficient, as rheumatologists would not be able to assess patients using psoriasis diagnostic criteria alone. Therefore, the Sponsor concluded that a PsA listing for ustekinumab was required.

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

5 Comparator

- 5.1 The previous major submission nominated adalimumab as the comparator. This main comparator is unchanged. An additional comparator, certolizumab pegol was included in this minor submission as a clinical and economic comparator, following its listing on the PBS on 1 April 2015.

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4) and health care professionals (12) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ustekinumab including that it improves quality of life, provides an alternative treatment option, and is more convenient than currently listed treatments which involve weekly injections.

Clinical trials

- 6.3 The previous major submission was based on two placebo-controlled trials of ustekinumab (PSUMMIT-1 and PSUMMIT-2) and two placebo-controlled trials of adalimumab (ADEPT trial and Genovese 2007). While the minor re-submission did not include any new clinical trials for ustekinumab and adalimumab, the efficacy results from a clinical trial for certolizumab (Table 1) were presented.

Table 1: Certolizumab trial presented in this current minor submission

Trial ID	Protocol title/ Publication title	Publication citation
RAPID	Mease, P, Fleischmann, R, et al. 2014, 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).	Ann Rheum Dis, 2014, 73:48-55.

Trial ID	Protocol title/ Publication title	Publication citation
	Van der Heijde, Fleischmann, et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol.	Ann Rheum Dis, 2014, 73: 233-237.

Source: November 2014 PBAC public summary document for certolizumab

6.4 The following differences were noted in the eligibility criteria and baseline characteristics of the trials (see Table 2):

- The adalimumab trials and one of the ustekinumab trials (PSUMMIT-1) enrolled patients who were naïve to TNF inhibitors, whereas one ustekinumab trial (PSUMMIT-2) and the certolizumab trial recruited both TNF inhibitor naïve and experienced patients.
- The definition of active PsA and baseline characteristics differed between the ustekinumab and certolizumab trials:
 - The definition of active PsA disease in the ustekinumab trials included five or more swollen joints and five or more tender joints.
 - The definition of active disease in the certolizumab trials is more in line with the adalimumab trials (i.e., three or more swollen joints and three or more tender joints).
 - The baseline mean swollen joint counts and baseline mean tender joint counts were higher in the ustekinumab patients compared to the certolizumab patients.
 - The baseline median C - reactive protein (CRP) values were also higher in the ustekinumab patients compared to the certolizumab patients.
 - The proportion of patients with psoriasis \geq 3% of body surface area was slightly higher in ustekinumab patients compared to certolizumab patients.
 - Therefore, the ustekinumab patients appear to have more severe disease compared to the certolizumab patients, and this may bias the results of the indirect comparison against ustekinumab.
- In the certolizumab trial, concomitant DMARDS permitted other than methotrexate, were sulfasalazine and leflunomide, whereas methotrexate was the only DMARD permitted in the ustekinumab and adalimumab trials. Baseline use of concomitant methotrexate was also slightly higher in the certolizumab trial compared to the ustekinumab trials. This may bias the results of the indirect comparison against ustekinumab.

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Table 2: Baseline characteristics of the ustekinumab, certolizumab and adalimumab trials varying across randomised groups (reported as mean (SD) unless otherwise stated)

Trial, treatment arm	Age (yrs)	Male, n (%)	White, n (%)	Weight (kg)	PsA duration (yrs)	Psoriasis duration (yrs)	Prior DMARD use n(SD) or %	CRP (mg/L)	ESR (mm/hr)	Tender joint count	Swollen joint count	Psoriasis ≥3% BSA, n (%)	PASI score	Concomitant MTX use n (%)	Prior TNF α inhibitor use n(%)
UST1: PSUMMIT-1															
PBO (n=206)	()	108 (52.4)	()	()	()	()	NR	() [^]	NR	()	()	146 (70.9)	()	96 (46.6)	0
UST 45mg (n=205)	()	106 (51.7)	()	()	()	()	NR	() [^]	NR	()	()	145 (70.7)	()	99 (48.3)	0
UST 90mg (n=204)	()	116 (56.9)	()	()	()	()	NR	() [^]	NR	()	()	149 (73.0)	()	101 (49.5)	0
UST2 : PSUMMIT-2															
PBO (n=104)	()	51 (49.0)	()	()	()	()	NR	() [^]	NR	()	()	80 (76.9)	()	49 (47.1)	62 (60)
UST 45mg (n=103)	()	48 (46.6)	()	()	()	()	NR	() [^]	NR	()	()	80 (77.7)	()	54 (52.4)	60(58)
UST 90mg (n=105)	()	49 (46.7)	()	()	()	()	NR	() [^]	NR	()	()	81 (77.1)	()	52 (49.5)	58(55)
CZP1: RAPID-PsA															
PBO (N=136)	47.3 (11)	57 (41.9)	132 (97)	82.6 (20)	7.9 (8)	NR	≥1: 99%	9 (0.2-131) [^]	34 (6-125) [^]	19.9 (14.7)	10.4 (7.6)	86 (63.2)	11.08	84 (61.8)	26 (19)
CZP 200mg (N=138)	48.2 (12)	64 (46.4)	135 (98)	85.8 (18)	9.6 (9)	NR	≥1:97%	7 (0.2-238) [^]	35 (5-125) [^]	21.5 (15.3)	11 (8.8)	89 (65.2)	12.88	88 (63.8)	31 (23)
CZP 400mg (N=135)	47.1 (11)	62 (45.9)	133 (99)	84.8 (19)	8.1 (8)	NR	≥1: 98%	8.7 (0.1-87) [^]	33(4-120) [^]	19.6 (14.8)	10.5 (7.5)	76 (56.3)	10.99	88 (65.2)	23 (17)
ADA1: ADEPT															
PBO (N=162)	49.2 (11)	89 (54.9)	152 (94)	85.5 (17)	9.2 (9)	17.1 (12.6)	1.5 (1.2)	14 (17)	NR	25.8 (18.0)	14.3 (11.1)	70 (43.2)	8.3	81 (50)	0
ADA (N=151)	48.6 (12)	85 (56.3)	147 (97)	86 (21)	9.8 (8)	17.2 (12)	1.5 (1.2)	14 (21)	NR	23.9 (17.3)	14.3 (12.2)	70 (46.4)	7.4	77 (51)	0
ADA2: Genovese 2007															
PBO (N=49)	47.7 (11)	25 (51.0)	46 (94)	88.5 (21)	7.2 (7)	13.8 (10.7)	2.1 (1.3)	9 (0-70) [^]	NR	29.3 (18.1)	18.4 (12.1)	NR	NR	23 (46.9)	0
ADA (N=51)	50.4 (11)	29 (56.9)	50 (98)	91.5 (23)	7.5 (7)	18 (13.2)	1.7 (0.9)	7 (0-45) [^]	NR	25.3 (18.3)	18.2 (10.9)	NR	NR	24 (47.1)	0

[^]=median (range)

Abbreviations: CZP=certolizumab pegol; ADA=adalimumab, UST=ustekinumab; BMI=body mass index; PsA=psoriatic arthritis; NR = not reported, BSA=body surface area; CRP=C-reactive protein; SD=standard deviation; IQR = interquartile range; MTX = methotrexate, NR = not reported; (s)DMARD=(synthetic) disease-modifying antirheumatic drug; TNF α =tumour necrosis factor alpha;

Comparative effectiveness

- 6.5 The minor submission nominated ACR50 response as the most relevant outcome for assessing PBS response to treatment for PsA. This has previously been accepted by the PBAC and is unchanged from the November 2014 major submission.
- 6.6 The minor submission compared initial response rates measured at 24 weeks for ustekinumab versus initial response rates measured at 12 weeks for the comparators.
- 6.7 The minor submission performed indirect comparisons using the unadjusted frequentist approach of ustekinumab versus adalimumab, ustekinumab versus certolizumab, and certolizumab versus adalimumab, via placebo as a common comparator.
- 6.8 The submission proposed that the effective price of ustekinumab was to be determined based on cost-minimisation of ustekinumab 45mg to certolizumab 200mg. Hence, the key comparison of interest is ustekinumab versus certolizumab.
- 6.9 The results of the indirect comparison of initial ACR50 response rates for ustekinumab versus certolizumab are summarised in Table 3. The results of the indirect comparison between ustekinumab and adalimumab have not been presented as they are the same as those presented in the November 2014 submission.
- 6.10 Although the minor submission stated that a comparison based upon treatment naïve patients was presented in Table 1, all patients in the P-SUMMIT-2 trial were inappropriately included. Thus, separate comparisons of all patients in the treatment-naïve population have also been presented in Table 3. In the treatment-naïve population of the P-SUMMIT-2 trial, due to small sample size, the ACR50 results of the comparison of ustekinumab versus placebo were no longer statistically significant.
- 6.11 The placebo ACR50 response rates were estimated to be on average 8.1%, 3.3% and 11.0% from the ustekinumab, adalimumab, and certolizumab trials, respectively. The placebo response rate was therefore higher in the ustekinumab and certolizumab trial compared with adalimumab.

Table 3: Summary of results of initial ACR50 response (at 24 weeks for ustekinumab, at 12 weeks for certolizumab) indirect comparison of ustekinumab versus certolizumab

Trial ID	Trials of ustekinumab				Trial of certolizumab ^e				Indirect estimate of effect ^c Indirect RR (95% CI)	Indirect estimate of effect ^c Indirect RD (95% CI)
	Treatment effect ^a RD (95% CI)	Treatment effect ^a RR (95% CI)	Ustekinumab 45 mg n /N (%)	Placebo n/N (%)	Placebo n/N (%)	Certolizumab (pooled) n /N (%)	Treatment effect ^b RR (95% CI)	Treatment effect ^b RD (95% CI)		
All patients					All patients				All patients	
PSUMMIT-1	0.16 (0.09, 0.23)		51/205 (24.9)	18/206 (8.7)	-	-	-	-	-	-
PSUMMIT-2	0.11 (0.02, 0.20)		18/103 (17.5)	7/104 (6.7)	-	-	-	-	-	-
RAPID	-	-	-	-	15/136 (11.0)	94/273 (34.4)	3.12 (1.88, 5.17)	0.23 (0.16, 0.31)	-	-
Pooled ^d	0.14 (0.09, 0.20)		-	-	-	-	3.12 (1.88, 5.17)	0.23 (0.16, 0.31)		
TNFα inhibitor naïve patients					TNFα inhibitor naïve patients				TNFα inhibitor naïve patients	
PSUMMIT-1	0.16 (0.09, 0.23)		51/205 (24.9)	18/206 (8.7)	-	-	-	-	-	-
PSUMMIT-2 ^f					-	-	-	-	-	-
RAPID	-	-	-	-	14/110 (12.7)	74/219 (33.8)	2.65 (1.57, 4.48)	0.21 (0.12, 0.30)	-	-
Pooled ^{d,f}			-	-	-	-	2.65 (1.57, 4.48)	0.21 (0.12, 0.30)		

ACR50 = American College of Rheumatology 50% improvement criteria; CI = confidence interval; n = number with event; N = number in group; RD = risk difference; RR = relative risk.

a ustekinumab 45mg over placebo

b certolizumab (pooled) over placebo

c inferred as ustekinumab over certolizumab

d pooled using the random effects model

e certolizumab (pooled) results from the RAPID trial were obtained from digital measurement of Figure 3 of the Mease et al. (2014) publication

f excluding treatment-experienced patients in PSUMMIT-2.

- 6.12 The results at Week 24 for ustekinumab and Week 12 for adalimumab illustrate that whilst both biologics were more effective than placebo in producing an ACR50 response, fewer patients would attain an ACR50 response with ustekinumab than adalimumab, even despite an additional 12 weeks of treatment with ustekinumab.
- 6.13 The results at Week 24 for ustekinumab and Week 12 for certolizumab illustrate that there was no significant difference in the number of patients who would attain an ACR50 response with ustekinumab and certolizumab, even despite an additional 12 weeks of treatment with ustekinumab.
- 6.14 The submission defined the minimum clinically important difference (MCID) in the outcome of ACR50 response as 0.29. This is derived from the lower bound of the 95% CI around the relative risk from an indirect comparison of adalimumab and etanercept, following the methodology used for MCID for ACR20 response (refer March 2010 PBAC public summary document for golimumab for methodology and Table 2, p19 of the submission for calculation of indirect relative risk for adalimumab versus etanercept). The relative risk for ustekinumab versus certolizumab is estimated as [redacted] ([redacted], [redacted]) and [redacted] ([redacted], [redacted]) for all patients, and the treatment-naïve population, respectively. Based on the MCID of 0.29, ustekinumab meets the non-inferiority criteria relative to certolizumab.

Comparative harms

- 6.15 No safety outcomes were presented in the minor submission. The PBAC, however, has previously accepted that the safety profiles of ustekinumab versus adalimumab and adalimumab versus certolizumab to be similar.

Clinical claim

- 6.16 The submission claimed inferior comparative effectiveness (in terms of ACR50 response) of ustekinumab compared with adalimumab.
- 6.17 The submission claimed non-inferior comparative effectiveness (in terms of ACR50 response) of ustekinumab compared with certolizumab.
- 6.18 The submission claimed inferior comparative effectiveness (in terms of ACR50 response) of certolizumab compared with adalimumab.
- 6.19 The evaluation noted that the interpretation of the results of these indirect comparisons require consideration:
- Ustekinumab patients appear to have more severe disease at baseline than certolizumab patients, which may indicate exchangeability issues;
 - The placebo (common reference) ACR50 response rates differed across ustekinumab, adalimumab and certolizumab trials, indicating exchangeability issues; and
 - The assessment of treatment response for certolizumab and adalimumab was at 12 weeks whilst response was assessed at 24 weeks for ustekinumab. Therefore, should patients not respond to ustekinumab they would be taking an extra

12 weeks of ineffective therapy, and experience a delay of up to 3 months in access to potentially more effective therapy.

Economic analysis

- 6.20 No economic comparison was presented in the minor re-submission. It was proposed that the price for ustekinumab will be based on a cost-minimisation analysis of ustekinumab 45mg versus certolizumab 200 mg.
- 6.21 The submission noted that such a price would be appropriately less than adalimumab and the other PBS listed bDMARDs (i.e. golimumab, infliximab and etanercept), reflecting inferiority against these agents.
- 6.22 Whilst a cost-minimised price of ustekinumab could be calculated from information on the price of certolizumab, the price was not presented in the minor re-submission, as it is currently only referenced confidentially. The submission anticipated that, should the PBAC recommend ustekinumab in PsA, such a price would be calculated.

Estimated PBS usage & financial implications

- 6.23 The submission did not present updated financial estimates for ustekinumab in PsA. The submission asserted, however, that PBS listing of ustekinumab at the certolizumab price would result in, at worst, no incremental cost to the PBS and, at best, would result in net cost savings. The submission based this assertion on the fact that ustekinumab would be cost-minimised against certolizumab, with the requested price being lower than the other PBS listed bDMARDs.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation regarding the request to list ustekinumab as an Authority Required benefit for the treatment of PsA, as acceptance of the submission's claim that ustekinumab is non-inferior to certolizumab pegol and inferior to adalimumab required the PBAC to accept that certolizumab pegol is also inferior to adalimumab, a finding which would be inconsistent with the PBAC recommendation for certolizumab from November 2014.

The PBAC considered this issue would need to be resolved before it could consider making a recommendation to list ustekinumab for psoriatic arthritis.

- 7.2 The PBAC recalled that it rejected the request to list ustekinumab for PsA in November 2014 on the basis of evidence of inferior effectiveness to adalimumab

(particularly in terms of joint response) and a lack of compelling evidence of clinical need.

- 7.3 The PBAC noted it previously accepted adalimumab as the appropriate comparator and accepted certolizumab as an additional comparator.
- 7.4 The PBAC noted that the pre-PBAC response clarified that the requested restriction is intended to position ustekinumab as a first and subsequent line therapy for patients with PsA for whom TNF α inhibitors are unsuitable. However it may not be appropriate for an inferior product to be included on an apparently equal basis in the “basket” of bDMARDs to which patients have access through the PBS, particularly as there is a limit on the number of products which patients can access, leading to the possibility of patient disadvantage.
- 7.5 The PBAC recalled that two ustekinumab dosing regimens were proposed in the November 2014 submission: 45 mg and 90 mg. The PBAC noted the resubmission only requested the 45 mg dose in line with the TGA’s subsequent recommendation on appropriate dosing, and considered this was appropriate.
- 7.6 The PBAC noted that the re-submission presented a revised clinical claim; that ustekinumab is inferior to adalimumab and non-inferior to certolizumab with regards to clinical effectiveness, based on ACR50. The PBAC considered that the clinical claim may not be adequately supported due to the following exchangeability issues between the ustekinumab and certolizumab trials:
- ustekinumab patients appear to have more severe disease at baseline than certolizumab patients;
 - the placebo (common reference) ACR50 response rates differed across ustekinumab, adalimumab and certolizumab trials; and
 - the assessment of treatment response for certolizumab and adalimumab was at 12 weeks whilst response was assessed at 24 weeks for ustekinumab. The PBAC agreed that should patients not respond to ustekinumab they would be taking an extra 12 weeks of ineffective therapy and experience a delay of up to 3 months in access to potentially more effective therapy. The pre-PBAC response claimed that only patients already unsuitable for TNF α inhibitor therapy would receive ustekinumab. However, this argument appeared to contradict the requested restriction which would allow for both first and subsequent line therapy.
- 7.7 The PBAC noted that the re-submission did not present data on comparative safety. However, the PBAC recalled that it previously accepted that the safety profiles of ustekinumab versus adalimumab and adalimumab versus certolizumab are similar.
- 7.8 The PBAC noted that the DUSC has not reviewed the utilisation of bDMARDs for PsA and requested that this be provided for the next meeting.

Outcome:
Deferred

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.