

4.07 USTEKINUMAB

45 mg/0.5 mL injection, 1 x 0.5 mL vial

Stelara®, Janssen-Cilag Pty Ltd.

1 Purpose of Application

- 1.1 PBAC reconsideration of the minor resubmission for ustekinumab in psoriatic arthritis (PsA) that was deferred by PBAC in July 2015 and that sought to address the issues raised when PBAC rejected an application for ustekinumab for PsA in November 2014 (refer ustekinumab Public Summary Document from the November 2014 meeting).

2 Requested listing

- 2.1 The July 2015 minor resubmission 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 Injection 45 mg/0.5 ml, 1x0.5 ml vial	1	2	Published: \$ [REDACTED] # Effective:*	Stelara Janssen-Cilag
<u>Continuing therapy</u>				
USTEKINUMAB Injection 45 mg/0.5ml, 1x0.5 ml vial	1	1	Published: \$ [REDACTED] # Effective: *	Stelara Janssen-Cilag

Authority required

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

#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.

* Effective price to be determined based on cost-minimisation of ustekinumab 45 mg to certolizumab 200 mg. 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.

For more detail on PBAC's view, see section 6 "PBAC outcome".

3 Background

- 3.1 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 the joint count 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 minutes – 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 400 mg (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.

- 3.2 In July 2015, 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 and inferior to adalimumab required the PBAC to accept that certolizumab is also inferior to adalimumab, a finding which would be inconsistent with the PBAC recommendation for certolizumab from November 2014. [REDACTED]

- 3.3 The Pharmaceutical Benefits Division of the Department of Health commissioned a report to review the claims presented in the minor resubmission.

4 Comparator

- 4.1 The PBAC has previously accepted adalimumab as the appropriate comparator and accepted certolizumab as an additional comparator.

For more detail on PBAC's view, see section 6 "PBAC outcome".

5 PBAC consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

- 5.3 The original 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 resubmission did not include any new clinical trials for ustekinumab and adalimumab, the efficacy results from one placebo-controlled trial of certolizumab were additionally presented to provide evidence for the additional comparator. This trial has previously been considered by the PBAC (PBAC Public Summary Document for certolizumab, November 2014).

Certolizumab trial presented in the minor resubmission

Trial IDs	Protocol title/Publication title	Publication citation
RAPID-PsA PSA001 NCT01087788	Mease, P, Fleischmann, R, 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).	Ann Rheum Dis 2014; 73:48-55.

Source: November 2014 PBAC Public Summary Document for certolizumab

Comparative effectiveness

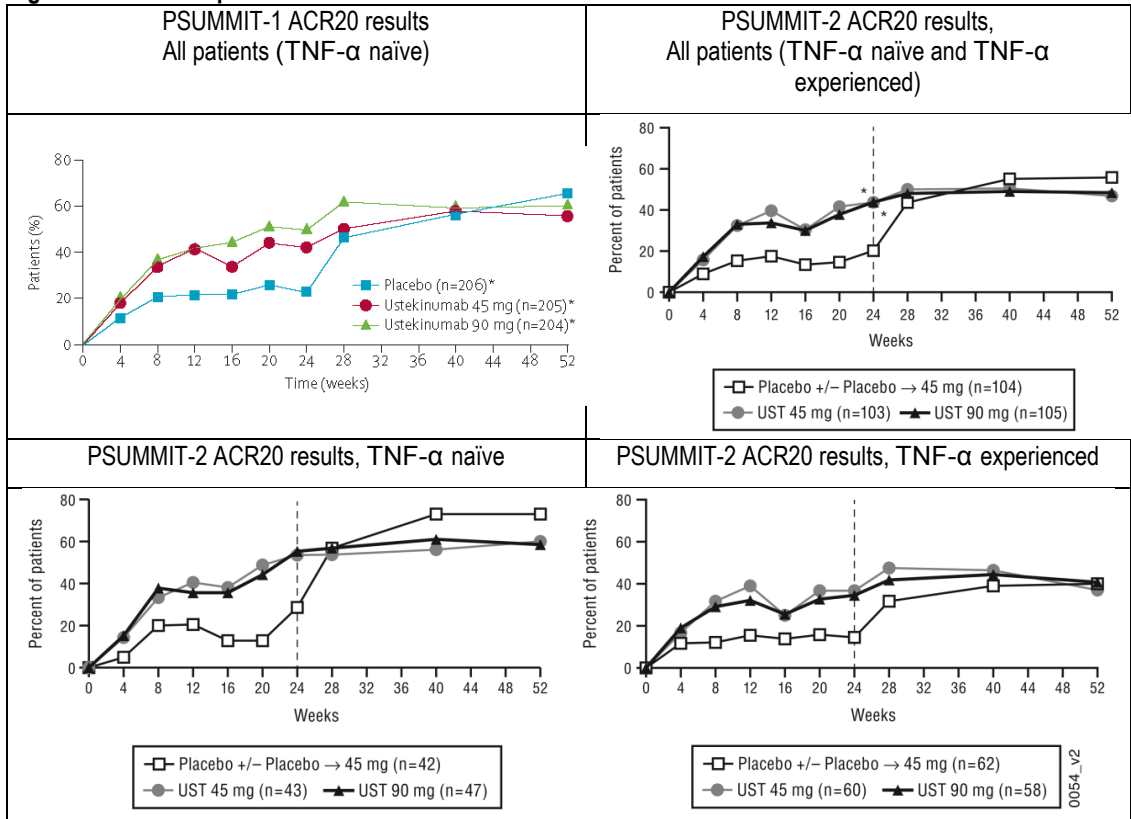
5.4 The PBAC previously accepted the ACR50 response as the most relevant outcome for assessing response to treatment for PsA.

5.5 Table 1 (p15) of the minor resubmission presented indirect comparisons of ustekinumab (UST) (at 24 weeks) to adalimumab (ADA) (at 12 weeks) and certolizumab (CZP) (at 12 weeks) for the outcome of ACR50¹ in tumour necrosis factor- α (TNF- α) inhibitor naïve patients. Two points of concern about the indirect comparisons were that:

- The comparison used data for UST at 24 weeks and ADA and CZP at 12 weeks. The primary outcome in the UST trials was ACR20 at 24 weeks, which is consistent with the proposed PBS restriction, indicating that assessment of the patient's response to the initial course of treatment must be made after at least 24 weeks so that there is adequate time for a response to be demonstrated, compared to assessment of patient's response on CZP or ADA at 12 weeks. Publications for the UST trials presented ACR20 response over time (Figure 1) and in both studies, the response rates across all patients were similar at 12 and 24 weeks for the recommended 45 mg dose. Assessment of patient response at 24 weeks as opposed to 12 weeks may have been justified based on subgroup results observed in TNF- α naïve patients enrolled in PSUMMIT-2, in which response rates increased between weeks 12 and 24 by 10-15%. However, this was not observed in the PSUMMIT-1 trial which only enrolled TNF- α naïve patients. Response rate curves were not presented for ACR50.
- That results included in the meta-analysis of UST trials included all patients enrolled in the PSUMMIT-2, rather than restricted to TNF- α naïve patients, as for the ADA and CZP data included in the analyses and in previous considerations of bDMARDs (including CZP) in psoriatic arthritis to the PBAC.

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. Lancet (London, England). 2013 Aug 31;382(9894):780-9.

Figure 1: ACR20 response rates from ustekinumab trials over time



Source: Figure 2A, McInnes et al¹ and Figures 1A, 1D and 1E, Ritchlin et al²

5.6 Table 1 below presents a comparison of UST (at 24 weeks) to ADA (at 24 weeks) and CZP (at 24 weeks) for the outcome of ACR50 restricted to TNF- α naïve patients to ensure comparisons across the same time point and in similar, TNF- α naïve, populations.

Table 1: Indirect comparison of UST, ADA and CZP in naïve patients at 24 weeks

	Ustekinumab, 45 mg (24 weeks)						Adalimumab (24 weeks)		Certolizumab (24 weeks)	
	PSUMMIT-1		PSUMMIT-2*		Meta-analysis		ADEPT		RAPID-PsA*	
	UST	PBO	UST	PBO	UST	PBO	ADA	PBO	CZP	PBO
ACR50, n/N (%)	51/205 (24.9)	18/206 (8.7)					59/153 (38.6)	10/162 (6.2)	91/219 (41.6)	16/110 (14.5)
RR [95% CI]	2.85 [1.72, 4.70]						6.25 [3.32, 11.76]		2.86 [1.77, 4.61]	
RD (%) [95% CI]	16 [9, 23]						32 [24, 41]		27 [18, 36]	
OR [95% CI]	3.46 [1.94, 6.17]						9.54 [4.65, 19.56]		4.18 [2.31, 7.57]	
Indirect comparison	UST 45 mg (treatment naïve) vs. CZP (treatment naïve)				UST 45 mg (treatment naïve) vs. ADA				CZP (treatment naïve) vs. ADA	
RR [95% CI]									0.46 [0.21, 1.01]	
RD (%) [95% CI]									-5 [-17, 7]	
OR [95% CI]									0.44 [0.17, 1.11]	

* treatment-naïve subgroup

** statistically significant result

ACR50=American College of Rheumatology 50% response; ADA=adalimumab; CZP=certolizumab; OR=odds ratio; RD=risk difference; RR=risk ratio; PBO=placebo; UST=ustekinumab

Source: Analyses were conducted during the evaluation, including random effects meta-analysis using Review Manager 5.3 ($I^2=0\%$) and indirect comparisons using CADTH Indirect Treatment Comparisons program, using data from McInnes et al¹, Ritchlin et al², Mease et al³ and Mease et al⁴.

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 Jun;73(6):990-9.

³ Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis and rheumatism*. 2005 Oct;52(10):3279-89.

⁴ 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 Jan;73(1):48-55.

- 5.7 Table 1 indicates that UST was significantly inferior to ADA in terms of the OR and RD, with a trend towards inferiority when measured by RR (upper limit = █████). It was noted that these results are at 24 weeks. The PBAC previously agreed that this was problematic as it could lead to patients experiencing a delay of up to 3 months in access to potentially more effective therapy.
- 5.8 CZP was not significantly inferior to ADA on any measure, although the upper limit for RR was 1.01. For the comparison of UST to CZP in treatment-naïve patients enrolled in the trials, RR and OR support the conclusion of non-inferiority, while RD provides less convincing support for this conclusion (██████████).
- 5.9 Table 2 below presents the comparison of UST and CZP for ACR50 at 24 weeks using all available data for all patients (i.e. both TNF- α naïve and TNF- α experienced) who were recruited to the trials. This was conducted to examine whether different conclusions are reached based on indirect comparisons of subgroup analyses or the ITT populations.

Table 2: Indirect comparison of UST and CZP in all patients at 24 weeks

	Ustekinumab, 45 mg (24 weeks)						Certolizumab (24 weeks)	
	PSUMMIT-1 Treatment naïve		PSUMMIT-2 Treatment experienced & naïve		Meta-analysis Treatment experienced & naïve		RAPID-PsA Treatment experienced & naïve	
	UST	PBO	UST	PBO	UST	PBO	CZP	PBO
ACR 50, n/N (%)	51/205 (24.9)	18/206 (8.7)	18/103 (17.5)	7/104 (6.7)	69/308 (22.4)	25/310 (8.1)	115/273 (42.1)	17/136 (12.5)
RR [95% CI]	2.85 [1.72, 4.70]		2.60 [1.13, 5.95]		2.78 [1.81, 4.27]		3.37 [2.11, 5.37]	
RD (%) [95% CI]	16 [9, 23]		11 [2, 20]		14 [9, 20]		30 [22, 38]	
OR [95% CI]	3.46 [1.94, 6.17]		2.93 [1.17, 7.37]		3.30 [2.02, 5.39]		5.09 [2.90, 8.94]	
Indirect comparison	UST 45 mg vs. CZP							
RR [95% CI]	0.83 [0.44, 1.56]							
RD (%) [95% CI]	-16 [-26, -6]**							
OR [95% CI]	0.65 [0.31, 1.36]							

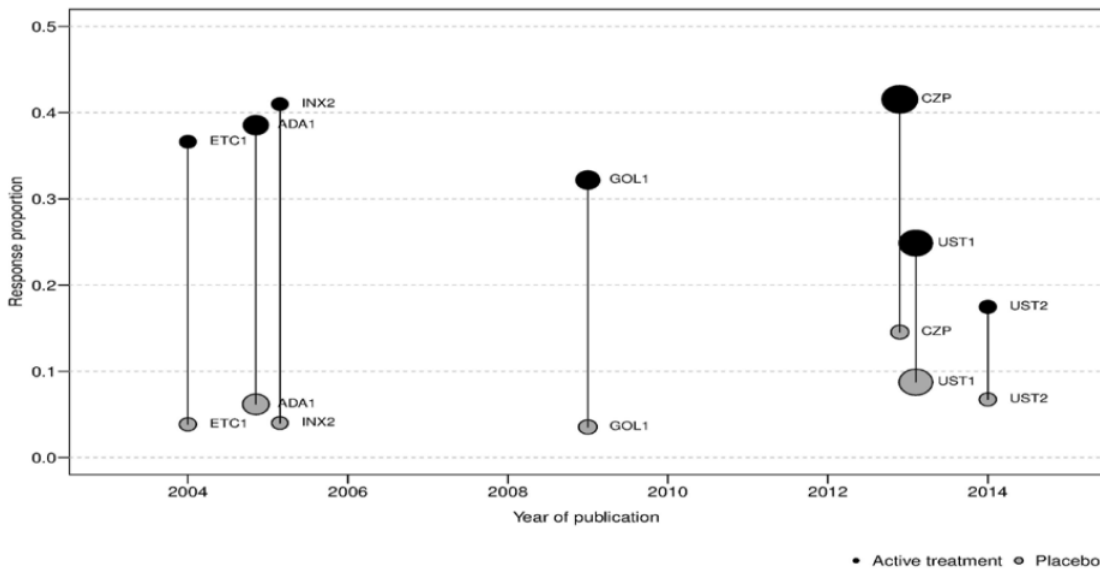
ACR50=American College of Rheumatology 50% response; CZP=certolizumab; OR=odds ratio; RD=risk difference; RR=risk ratio; PBO=placebo; UST=ustekinumab
 Source: Analyses were conducted during the evaluation, including random effects meta-analysis using Review Manager 5.3 ($I^2=0\%$) and indirect comparisons using CADTH Indirect Treatment Comparisons program, using data from McInnes et al¹, Ritchlin et al² and Mease et al³.

- 5.10 In the comparison of UST and CZP using all patients enrolled in the trials (i.e. both TNF- α naïve and TNF- α experienced), RR and OR support the conclusion of non-inferiority between these products, however the RD scale suggests that UST is inferior to CZP (-16, 95% CI: -26, -6) (Table 2).
- 5.11 The results of the indirect comparisons based on the TNF- α naïve subgroup and ITT populations support the conclusion of non-inferiority of ustekinumab to certolizumab on the basis of RR and OR. Indirect comparisons on the RD scale are less supportive of this conclusion: in the TNF- α naïve subgroup, the upper limit of the

95% CI was [redacted] and UST was significantly inferior to CZP in indirect comparisons based on the ITT population.

- 5.12 As the claim is made on the basis of indirect comparisons, there is an assumption of exchangeability between the populations and settings in the trials that are being indirectly compared. As it appears that the CZP trial in psoriatic arthritis is clinically heterogeneous to the UST evidence in terms of placebo response rate then this assumption of exchangeability may not hold.
- 5.13 The review of the minor resubmission additionally presented a plot of the actual response rates in the trials for ACR50, at 24 weeks, reproduced in Figure 2, below, for TNF- α naive patients in all trials, except PSUMMIT-2 (as data for TNF- α naive patients could not be separately identified). It was noted that the absolute response in the active treatment arm of the CZP trial was similar to responses observed with the other listed bDMARDs, while response rates due to active treatment in the UST trials were substantially lower. The placebo response rate in the CZP trial was higher than the placebo rates in all of the other trials. Without understanding the reason for the higher placebo response rate observed in the CZP trial, the review concluded that it is 'impossible' to determine whether the usual assumption of homogeneous effects in the RR or OR scales is reasonable (Attachment 1, pp5-6).

Figure 2: Actual ACR50 response rates in the included trials at 24 weeks
ACR50 at 24 weeks by year of publication



Source: Figure 1, p6 of report “Statistical issues surrounding the evaluation of biological disease modifying anti-rheumatic drugs (bDMARDs) for psoriatic arthritis” (Attachment 1)

ETC = etanercept, ADA = adalimumab, INX = infliximab, GOL = golimumab, CZP = certolizumab, UST = ustekinumab

- 5.14 There is uncertainty in the evidence presented to support the claim of non-inferiority of UST and CZP. This is due to uncertain exchangeability of the trials as indicated by apparent differences in the placebo arms of the trials. The placebo ACR50 response rate at 24 weeks was observed to be 15% in the CZP trial and 7-9% in the UST trials. The placebo response rates were also substantially higher than those observed in the ADA, etanercept, infliximab and golimumab trials (4-6%). It was noted that UST

and CZP trials were clustered together chronologically and so may be more comparable than the cluster of earlier trials of bDMARDs.

Comparative harms

- 5.15 The PBAC has previously accepted that the safety profiles of ustekinumab versus adalimumab and adalimumab versus certolizumab are similar.

Clinical claim

- 5.16 The submission claimed that ustekinumab is inferior to adalimumab and non-inferior to certolizumab with regards to clinical effectiveness.
- 5.17 In July 2015, 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.
- 5.18 The commissioned report concluded that it is difficult to support the claim that ustekinumab and certolizumab are non-inferior to each other, noting that it is also difficult to conclude that ustekinumab is definitely inferior.

For more detail on PBAC's view, see section 6 "PBAC outcome".

Economic analysis

- 5.19 It was previously proposed that the price for ustekinumab be based on a cost-minimisation analysis of ustekinumab 45 mg versus certolizumab 200 mg, both given according to the regimens recommended in their Product Information.

For more detail on PBAC's view, see section 6 "PBAC outcome".

Estimated PBS usage & financial implications

- 5.20 A DUSC review on the utilisation of bDMARDs for PsA has been conducted and was considered at the November 2015 PBAC meeting.

6 PBAC outcome

- 6.1 The PBAC recommended an Authority Required listing of ustekinumab for the treatment of psoriatic arthritis (PsA) on a cost-minimisation basis with certolizumab. The equi-effective doses are UST 45 mg administered at weeks 0, 4 and then every 12 weeks thereafter equals CZP 400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks or 400 mg every 4 weeks.
- 6.2 The PBAC considered that the restriction as requested is appropriate, despite accepting that ustekinumab is non-inferior to certolizumab and inferior to adalimumab, as it will allow clinicians to choose from a range of bDMARDs for the treatment of individual patients.
- 6.3 The PBAC considered that certolizumab and adalimumab are the appropriate comparators.
- 6.4 The PBAC recalled it previously accepted that the safety profiles of ustekinumab versus adalimumab and adalimumab versus certolizumab are similar.
- 6.5 The PBAC accepted the clinical claim as presented in the July 2015 resubmission that UST is non-inferior to CZP and inferior to ADA. This places both UST and CZP in the south-west quadrant of the cost-effectiveness plane compared to other bDMARDs for PsA.
- 6.6 The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that ustekinumab and certolizumab for the treatment of PsA should be treated as interchangeable on an individual patient basis.
- 6.7 The PBAC advised that ustekinumab is not suitable for prescribing by nurse practitioners.
- 6.8 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 6.9 The PBAC noted flow-on restriction changes to adalimumab, certolizumab, etanercept, golimumab and infliximab.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
USTEKINUMAB Injection 45 mg/0.5 mL, 1 x 0.5 mL vial	1	2	Stelara	Janssen-Cilag

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

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Episodicity:	-
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<p>Must be treated by a rheumatologist; OR</p> <p>Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.</p>
Clinical criteria:	<p>Patient must have severe active psoriatic arthritis; AND</p> <p>Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR</p> <p>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 for this condition; AND</p> <p>Patient must have failed to achieve adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months; AND</p> <p>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</p> <p>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</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction.</p>
Population criteria:	Patient must be an adult
Foreword	-
Definitions	-
Prescriber Instructions	<p>For the purpose of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or ustekinumab.</p> <p>Where treatment with methotrexate, sulfasalazine or leflunomide is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application.</p> <p>Where intolerance to treatment with methotrexate, sulfasalazine or leflunomide developed during the relevant period of use, which was of a severity to necessitate permanent treatment withdrawal, details of the degree of this toxicity must be provided at the time of application.</p> <p>The following initiation criteria indicate failure to achieve an adequate response and</p>

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	<p>must be demonstrated in all patients at the time of the initial application:</p> <p>an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L; and either</p> <p>(a) An active joint count of at least 20 active (swollen and tender) joints; or (b) At least 4 active joints from the following list of major joints: i) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or ii) Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.</p> <p>The authority application must be made in writing and must include: 1) A completed authority prescription form; and 2) A completed psoriatic arthritis PBS Authority Application – Supporting Information Form; and 3) A signed patient acknowledgement.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Cautions	-

Name, Restriction, Manner of administration and form	Max. Qty	№ of Rpts	Proprietary Name and Manufacturer	
USTEKINUMAB Injection 45 mg/0.5 mL, 1 x 0.5 mL vial	1	2	Stelara	Janssen-Cilag

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 2 (change or recommencement of treatment)
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<p>Must be treated by a rheumatologist; OR</p> <p>Must be treated by a clinical immunologist with expertise in the management of</p>

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	psoriatic arthritis.
Clinical criteria:	<p>Patient must have a documented history of severe active psoriatic arthritis; AND</p> <p>Patient must have received prior PBS-subsidised treatment with a biological agent for this condition in the Treatment Cycle; AND</p> <p>Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological agents within this Treatment Cycle; AND</p> <p>Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug during the current Treatment Cycle; AND</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction.</p>
Population criteria:	Patient must be an adult
Foreword	-
Definitions	-
Prescriber Instructions	<p>For the purpose of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or ustekinumab.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> 1) A completed authority prescription form; and 2) A completed Psoriatic Arthritis PBS Authority Application – Supporting Information Form. <p>Application for a patient who has previously received PBS-subsidised treatment with this drug within this Treatment Cycle and who wishes to recommence therapy with this drug within this same Cycle must be accompanied by evidence of a response to the patient's more recent course of PBS-subsidised treatment with this drug.</p> <p>Where the most recent course of PBS-subsidised treatment was approved under either of the initial treatment restrictions (i.e. for patients with no prior PBS-subsidised biological therapy or, under this restriction, for patients who have received previous PBS-subsidised biological therapy), the patient must have been assessed for response following a minimum of 12 weeks of therapy. This assessment must have been submitted no later than 4 weeks from the date that course was ceased.</p> <p>Where the most recent course of PBS-subsidised treatment with this drug was approved under the continuing treatment criteria, the patient must have been assessed for response, and the assessment submitted no later than 4 weeks from the date that course was ceased.</p> <p>Where a response assessment was no submitted within these timeframes, the patient will be deemed to have failed to respond to treatment.</p> <p>An adequate response to treatment is defined as:</p> <p>An erythrocyte sedimentation rate (ESR) no greater than 25 mm per hour or a C-reactive protein (CRP) level no greater than 15 mg per L or either marker reduced by at least 20% from baseline; and</p> <p>Either of the following:</p>

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	<p>a) A reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or</p> <p>b) A reduction in the number of the following major active joints, from at least 4, by at least 50%:</p> <p>i) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or</p> <p>ii) Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>The assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of treatment and submitted to the Department of Human Services no later than 4 weeks from the cessation of the treatment course. If the response assessment is not submitted within these timeframes, the patient will be deemed to have failed this course of treatment.</p> <p>Details of toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 3 months treatment with methotrexate, sulfasalazine or leflunomide can be found on the Department of Human Services website (www.humanservices.gov.au).</p> <p>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Cautions	-

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
USTEKINUMAB Injection 45 mg/0.5 mL, 1 x 0.5 mL vial	1	1	Stelara	Janssen-Cilag

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Continuing treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<p>Must be treated by a rheumatologist; OR</p> <p>Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.</p>
Clinical criteria:	<p>Patient must have a documented history of severe active psoriatic arthritis; AND</p> <p>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;</p> <p>AND</p> <p>Patient must demonstrate, at the time of application, an adequate response to treatment with this drug; AND</p> <p>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.</p>
Population criteria:	Patient must be an adult
Foreword	-
Definitions	-
Prescriber Instructions	<p>For the purpose of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or ustekinumab.</p> <p>An adequate response to treatment is defined as:</p> <p>An erythrocyte sedimentation rate (ESR) no greater than 25 mm per hour or a C-reactive protein (CRP) level no greater than 15 mg per L or either marker reduced by at least 20% from baseline; and</p> <p>Either of the following:</p> <ul style="list-style-type: none"> a) A reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or b) A reduction in the number of the following major active joints, from at least 4, by at least 50%: <ul style="list-style-type: none"> i) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or ii) Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). <p>The same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be provided for all subsequent continuing treatment applications.</p> <p>All application for continuing treatment with this drug must include a measurement of response to the most recent course of PBS-subsidised therapy. This assessment must be submitted no later than 4 weeks from the cessation of that treatment course.</p>

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	<p>If the application is the first application for continuing treatment with this drug, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with the initial treatment course.</p> <p>Where a response assessment is not submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> 1) A completed authority prescription form; and 2) A completed Psoriatic Arthritis PBS Authority Application – Supporting Information Form. <p>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Cautions	-

The following note will appear on all above restrictions:

Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au
Applications for authority to prescribe should be forwarded to:

Department of Human Services
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

The following note will be added to all above restrictions and flow-on changes made to adalimumab, certolizumab, etanercept, golimumab and infliximab:

TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE PSORIATIC ARTHRITIS

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological agents adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and ustekinumab for adult patients with severe active psoriatic arthritis.

Patients are eligible for PBS-subsidised treatment with only 1 of the above biological agents at any 1 time.

Where the term 'biological agents' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and ustekinumab only.

Patients receiving PBS-subsidised treatment for psoriatic arthritis are able to commence a 'Biological Treatment Cycle' (Cycle), where they may trial biological agents without having to experience a disease flare when swapping to the alternate agent. Under these interchangeability arrangements, within a single Cycle, patients may receive long-term treatment with a biological agent as long as they sustain a response to therapy.

Following demonstration of response to initial treatment, these biological agents are available under the PBS for continuing treatment as set out in the continuing treatment restriction for each agent.

Once patients have either failed or ceased to sustain a response to treatment 3 times, they are deemed to have completed a single Cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological therapy before they are eligible to commence another Cycle [further details are under '(5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy' below].

The duration of the break in therapy will be measured from the date the last approval for PBS-subsidised treatment was granted in the most recent Cycle to the date of the first application for initial treatment with a biological agent under the new Cycle.

Within the same Cycle, patients are not allowed to fail, or cease to respond to, the same PBS-subsidised biological agent more than once. Therefore once a patient fails to meet the response criteria for any biological agent, they must change to an alternate agent which they have not previously failed, if they wish to continue PBS-subsidised biological treatment.

Patients for whom a break in PBS-subsidised therapy of less than 5 years has occurred, and, who have failed therapy fewer than 3 times within a particular treatment Cycle, as defined in the relevant restriction, may commence a further course of treatment within that Cycle.

Patients for whom a break in PBS-subsidised therapy of 5 years or more has occurred, and, who have failed therapy fewer than 3 times within a particular treatment Cycle, as defined in the relevant restriction, are eligible to commence a new Cycle.

There is no limit to the number of Biological Treatment Cycles a patient may undertake in their lifetime.

How to prescribe biological agents for the treatment of severe active psoriatic arthritis.

(1) Initial treatment.

Applications for initial treatment should be made where:

- (i) patients have received no prior PBS-subsidised biological treatment and wish to commence such therapy (Initial 1); and
- (ii) patients have received prior PBS-subsidised biological therapy and wish to trial an alternate agent (Initial 2) [further details are under 'Swapping therapy' below]; and

(iii) patients wish to re-commence treatment with a specific biological agent following a break in PBS-subsidised therapy with that specific agent (Initial 2).

All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, golimumab and ustekinumab, 18 to 20 weeks of therapy for certolizumab pegol (depending upon the dosing regimen), and 22 weeks of therapy for infliximab. It is recommended that patients be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological agent supply.

Patients must be assessed for response to any course of PBS-subsidised initial treatment following a minimum of 12 weeks of therapy and this assessment must be submitted to the Department of Human Services no later than 4 weeks from the date that course was ceased. Where a response assessment is not submitted within these timeframes, patients will be deemed to have failed to respond to treatment with that biological agent.

Grandfather patients - certolizumab pegol only.

For patients who commenced treatment with certolizumab pegol for psoriatic arthritis prior to 1 April 2015, applications for initial PBS-subsidised treatment as continuing therapy may be made under the relevant initial treatment restriction (Initial 3). These patients access the PBS interchangeability arrangements in the same way as new patients who have not been treated with any biological agent prior to PBS listing of that agent.

Applications for initial PBS-subsidised treatment for grandfather patients will provide for a maximum of 24 weeks of treatment for all agents. Approval will be based on the criteria included in the relevant restriction.

(2) Continuing treatment.

Following the completion of an initial treatment course with a specific biological agent, patients may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment.

Patients are eligible to receive continuing biological treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

Patients must be assessed for response to a course of continuing therapy, and the assessment must be submitted to the Department of Human Services no later than 4 weeks from the date that course was ceased. Where a response assessment is not submitted within these timeframes, patients will be deemed to have failed to respond to treatment with that biological agent.

(3) Swapping therapy.

Once an authority for initial treatment with the first PBS-subsidised biological agent is approved, patients may swap to an alternate biological agent without having to re-qualify with respect to either the indices of disease severity (i.e. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and active joint count) or the prior non-biological therapy requirements.

Patients may swap to an alternate biological agent at any time, regardless of whether they are receiving therapy (initial or continuing) with a biological agent at the time of the application or not.

Within a Treatment Cycle patients may alternate between therapy with any biological agent of their choice (1 at a time) providing:

- (i) they have not received PBS-subsidised treatment with that particular biological agent previously; or
- (ii) they have demonstrated an adequate response to that particular biological agent if they have previously trialed it on the PBS; and
- (iii) they have not previously failed to respond to treatment 3 times in this Treatment Cycle.

To ensure patients receive the maximum treatment opportunities allowed under the interchangeability arrangements, it is important that they are assessed for response to every course of treatment approved, within the timeframes specified in the relevant restriction.

To avoid confusion, applications for patients who wish to swap to an alternate biological agent should be accompanied by the approved authority prescription or remaining repeats for the biological agent the patient is ceasing.

- (4) Baseline measurements to determine response.

The Department of Human Services will determine whether a response to treatment has been demonstrated based on the baseline measurements of the indices of disease severity submitted with the first authority application for a biological agent. However, prescribers may provide new baseline measurements any time that an initial treatment application is submitted within a treatment Cycle and these revised baseline measurements will be used to assess response.

To ensure consistency in determining response, the same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be provided for all subsequent continuing treatment applications. Therefore, where only an ESR or CRP level is provided at baseline, an ESR or CRP level respectively must be provided to determine response. Similarly, where the baseline active joint count is based on total active joints (i.e. 20 or more active joints), response will be determined according to a reduction in the total number of active joints.

- (5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy.

Patients who wish to trial a second or subsequent treatment Cycle following a break in PBS-subsidised biological therapy of at least 5 years, must requalify for initial treatment with respect to both the indices of disease severity. Patients must have received treatment with methotrexate and sulfasalazine or leflunomide, at an adequate dose, for a minimum of 3 months at the time the ESR or CRP levels and the active joint counts are measured.

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.