PUBLIC SUMMARY DOCUMENT
Product: Ustekinumab (rmc), solution for injection, 45 mg in 0.5 mL, Stelara®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission requested an authority required PBS listing for the treatment of severe chronic plaque psoriasis in patients who meet the PBS criteria for treatment with a biologic.

2. Background

This drug has not previously been considered by the PBAC.

3. Registration Status

Ustekinumab was TGA registered on 29 July 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

4. Listing Requested and PBAC's View

The submission requested a listing consistent with the other biologics PBS listed for the treatment of chronic plaque psoriasis with two exceptions:

- Dosing of ustekinumab is weight based; and
- An initial treatment period of 28 weeks.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Psoriasis is a chronic disease with predominantly skin and joint manifestations affecting approximately 2% of the population. Plaque psoriasis is the most common form affecting approximately 80-90% of patients. The major manifestation is chronic inflammation of the skin characterised by disfiguring, scaling and erythematous plaques that may be painful or pruritic.

Ustekinumab will provide clinicians with an alternative biological therapy, with a different mechanism of action, for patients with severe chronic plaque psoriasis whose condition is refractory to other systemic treatments or phototherapy.

6. Comparator

The submission nominated etanercept as the main comparator. The submission also provided comparisons with infliximab, adalimumab and efalizumab.

The PBAC agreed that etanercept was the appropriate main comparator, and that adalimumab and infliximab were appropriate secondary comparators. The PBAC noted that comparisons with efalizumab were also provided however they were not considered relevant due to withdrawal of efalizumab from the Australian market.

7. Clinical Trials

The submission presented one randomised trial (the ACCEPT trial) comparing ustekinumab 45 mg and 90 mg with etanercept 100 mg/week in patients with chronic plaque psoriasis.

As the etanercept dose used in the direct randomised trial is double the PBS-subsidised dose (50 mg/week), the submission also presented an indirect comparison using placebo as a common comparator of two randomised controlled trials of ustekinumab 45 mg and 90 mg (PHOENIX 1 & 2), four trials of etanercept 50 mg/week, four trials of infliximab used at 5 mg/kg and three trials of adalimumab used at a maintenance dose of 40 mg every other week.

The key trials published at the time of submission are shown in the table below:

Trial ID/First author	Protocol title/ Publication title	Publication citation
ACCEPT (2008) Griffiths CEM, Strober B, van der Kerkhof PCM et al.	A Phase 3, multicentre, randomized study comparing ustekinumab and etanercept for the treatment of moderate to severe plaque psoriasis [Poster]	Presented at: 17th Congress of European Academy of Dermatology and Venereology, September 17-21, 2008. Paris, France.
PHOENIX I Leonardi CL et al	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)	The Lancet 2008; 371: 1665-1674.
PHOENIX II Papp KA et al	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)	The Lancet 2008; 371: 1675-1684.
Leonardi et al 2003	Etanercept as Monotherapy in Patients with Psoriasis	New England Journal of Medicine 2003; 349:2014-2022
Papp et al, 2005	A global phase III randomised controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	British Journal of Dermatology 2005; 152:1304-1312
Gottlieb et al 2003	A Randomised Trial of Etanercept as Monotherapy for Psoriasis	Archives of Dermatology 2003; 139:1627-1632
van de Kerkhof et al 2008	Once weekly administration of etanercept 50mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomised controlled trial with open-label extension.	British Journal of Dermatology 2008; 159:1177-1185
Chaudhari et al, 2001	Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.	The Lancet 2001; 357:1842-1847
Gottlieb et al 2004	Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomise, double-blind, placebo-controlled trial	Journal of the American Academy of Dermatology 2004; 51(4): 534-542
Menter et al 2007 (EXPRESS II)	A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis.	Journal of the American Academy of Dermatology 2006; 56(1): 31e1-31e15
Reich et al, 2005 (EXPRESS)	Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.	The Lancet 2005; 366: 1367-1374
Menter et al, 2008 (REVEAL)	Adalimumab therapy for moderate to severe psoriasis: A randomised, controlled phase III trial.	Journal of the American Academy of Dermatology 2008; 58(1): 106-115
Saurat et al	Efficacy and safety results from the randomised	British Journal of

Trial ID/First author	Protocol title/ Publication title	Publication citation
2008 (CHAMPION)	controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis.	Dermatology 2007; 158:558-566
Gordon et al 2006 (M02-528)	Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomised controlled trial and open-label extension study	Journal of the American Academy of Dermatology 2006; 55(4): 598-606

8. Results of Trials

Three analyses were presented:

- A direct comparison of ustekinumab versus etanercept 100 mg per week (not the dose reimbursed on the PBS);
- An indirect comparison of ustekinumab verus etanercept 50 mg per week (base case); and
- An indirect comparison of ustekinumab versus infliximab.

The primary outcome of each of the trials was PASI 75 response at 12 weeks, with the exception of the infliximab trial reported by Chaudhari et al (2001) where it was a secondary outcome.

The results of PASI 75 response in the ACCEPT trial are presented in the table below. The submission requested that patients weighing ≤100 kg be treated with 45 mg and those weighing >100 kg be treated with 90 mg ustekinumab.

PASI 75 response at 12 weeks in the ACCEPT Trial (ITT)

Outcome	Ustekinumab 45 mg	Ustekinumab 90 mg	Etanercept 100mg/week	OR (95% CI) versus etanercept	
				45 mg	90 mg
PASI 75	141/209 (67.5)	256/347 (73.8)	197/347 (56.8)	**1.58 (1.10, 2.26)**	**2.14 (1.56, 2.95)**
Responders at week 12 (ITT) who had an inadequate response to, intolerance to, or contraindication to 3 conventional systemic therapies (representative of the PBS eligible population)					
PASI 75	17/31 (54.8)	34/47 (72.3)	20/52 (38.5)	1.94 (0.79,4.79)	**4.18 (1.79,9.78)**

ITT analysis – patients randomly assigned to ustekinumab 45 mg or 90 mg. Dosing was not weight based.

The results from the ACCEPT trial indicated that statistically significantly more patients achieved a PASI 75 response at 12 weeks when treated with 45 mg or 90 mg ustekinumab compared with etanercept 100 mg/week in the ITT population (not dosed according to weight). An analysis for patients dosed according to the PI recommendations (i.e. ≤ 100 kg 45 mg; > 100 kg 90 mg) demonstrated that statistically significant more patients achieved a PASI 75 response at 12 weeks when:

- Patients weighing ≤ 100 kg were treated with 45 mg ustekinumab; and
- Patients weighing >100 kg were treated with 90 mg ustekinumab. However, for patients weighing > 100 kg treated with 45 mg ustekinumab, ustekinumab is not superior to etanercept.

For patients representative of the PBS eligible population based on failure of previous systemic therapies, a statistically significantly greater proportion of patients achieved a PASI

75 response when treated with 90 mg ustekinumab, but not 45 mg (ITT population, not dosed according to weight).

The results of the PASI 75 response rates at 12 weeks for the PHOENIX trials and those reported for etanercept 50 mg/week and infliximab and an indirect comparison using placebo as the common reference is presented in the tables below.

Indirect comparison of ustekinumab and etanercept for PASI 75 response at 12 weeks, n/N (%)

Trial	Treatment effect OR (95% CI)	Usteki	Placebo	Etanercept 50mg/week	Treatment effect OR (95% CI)	Indirect OR (95% CI)
ITT (Primary outcome)						
PHOENIX 1	**61.93 (29.91, 128.22)**	341/511 (66.7)	8/255 (3.1)	-		
PHOENIX 2	**65.16 (38.08, 111.52)**	584/820 (71.2)	15/410 (3.7)	-		
Meta-analysis	**64.00 (41.54, 98.61)**					
ITT						
Gottlieb 2003		-	1/55 (1.8)	17/57 (29.8)	**22.95 (2.93, 179.67)**	
Papp 2005		-	6/193 (3.1)	67/196 (34.2)	**16.19 (6.82, 38.44)**	
van der Kerkhof 2008		-	1/46 (2.2)	36/96 (37.5)	**27.00 (3.57, 204.40)**	
Leonardi 2003		-	6/166 (3.6)	55/162 (34.0)	**13.71 (5.70, 32.96)**	
Meta-analysis					**16.14 (9.16, 28.44)**	
ITT based indirect OR						**3.97 (1.95, 8.09)**

Bolded typography indicates statistically significant differences
ITT analysis – patients randomly assigned to ustekinumab 45 mg or 90 mg. Dosing was not weight based.

The PBAC considered the indirect comparison of the ustekinumab (PHOENIX) trials with the etanercept 50 mg/week trials provided the base case for the submission as the etanercept dose is equivalent to the current PBS subsidised dose of etanercept. The results of the indirect comparison for PASI 75 response rates at 12 weeks for the ITT and weight based dosing analyses indicated that statistically significantly more patients achieved a PASI 75 response when treated with ustekinumab compared with etanercept 50 mg/week.

Indirect comparison of ustekinumab (12 weeks) and infliximab for PASI 75 response at 10 weeks, n/N (%)

Trial	Treatment effect OR (95% CI)	Usteki	Placebo	Infliximab	Treatment effect OR (95% CI)	Indirect OR (95% CI)
ITT						
PHOENIX 1	**61.93 (29.91, 128.22)**	341/511 (66.7)	8/255 (3.1)	-		
PHOENIX 2	**65.16 (38.08, 111.52)**	584/820 (71.2)	15/410 (3.7)	-		
Meta-analysis	**64.00 (41.54, 98.61)**					

Trial	Treatment effect OR (95% CI)	Usteki	Placebo	Infliximab	Treatment effect OR (95% CI)	Indirect OR (95% CI)
ITT (10 wk outcome)						
Reich et al 2005		-	2/77 (2.6)	242/301 (80.4)	**153.81 (36.71, 644.55)**	
Chaudhari		-	2/11 (18.2)	9/11 (81.2)	**20.25 (2.32, 176.79)**	
Menter et al 2007		-	4/208 (1.9)	237/314 (75.5)	**156.97 (56.47, 436.36)**	
Gottlieb et al 2004		-	3/51 (5.9)	87/99 (87.9)	**116.00 (31.20, 431.34)**	
Meta-analysis					**118.57 (60.39, 232.83)**	
ITT based indirect OR						0.581 (0.107,3.140)

Bolded typography indicates statistically significant differences
ITT analysis – patients randomly assigned to ustekinumab 45 mg or 90 mg. Dosing was not weight based.

The results from the indirect comparison of the PHOENIX trials with the infliximab trials indicated no statistically significant differences in the proportion of patients achieving a PASI 75 response at 12 weeks when treated with ustekinumab compared with infliximab (10 weeks) in the indirect comparisons of the ustekinumab ITT and dosed according to weight populations.

The safety results of the ACCEPT trial indicated that patients treated with ustekinumab 45 mg had a statistically significantly increased incidence of back pain, but statistically lower incidence of general disorders and administration site conditions, injection site erythema and injection site swelling compared with etanercept 100 mg/week.

The safety results of the PHOENIX trials and the indirect comparisons of ustekinumab and etanercept and infliximab showed no differences between ustekinumab and etanercept in the proportion of patients experiencing at least one adverse event. Statistically significantly fewer patients treated with ustekinumab experienced at least one adverse event compared with those treated with infliximab.

9. Clinical Claim

The submission described ustekinumab as:

- Superior in terms of comparative effectiveness and equivalent in terms of comparative safety over etanercept 50 mg/week.
- Non-inferior in terms of comparative effectiveness at 12 weeks with superior efficacy beyond 24 weeks and superior in terms of comparative safety (significantly fewer AEs and equivalent SAEs) over infliximab.

The PBAC agreed that, based on the supporting data provided in the submission, ustekinumab is more effective and no worse in comparative safety compared with etanercept 50 mg/week at 12 weeks. However, the PBAC did not accept the claim that ustekinumab is more effective and superior in terms of comparative safety than infliximab at 24 weeks as no statistical analyses were presented due to asymmetry of available data to confirm this claim. Also assessment of long-term safety data of ustekinumab compared with etanercept and infliximab is unknown as the longest follow-up for safety for infliximab and etanercept is 52 weeks.

10. Economic Analysis

The submission presented a stepped economic evaluation.

Step 1 of the economic evaluation was a cost-effectiveness analysis, where the incremental cost per additional PASI 75 responder over 12 weeks was generated.
Step 2 of the analysis involved a cost-utility analysis: an extrapolation of outcomes beyond the 12-week time horizon examined in the trials to a 5-year time horizon; valuation of the outcomes of PASI 75 response and failure to respond; and discounting of both costs and benefits incurred beyond the first year. The only resources considered in these analyses were drug and drug administration costs associated with first-line therapy.
Step 3 of the analysis introduced costs and benefits associated with second and third-line therapy and best supportive care.

Three sets of analyses were presented in the submission based directly on the results of:

(i) The direct comparison of ustekinumab and etanercept 100 mg/week (dose not reimbursed under the PBS);
(ii) The indirect comparison of ustekinumab and etanercept 50 mg/week (base case); and
(iii) The indirect comparison of ustekinumab and infliximab.

Costs for the management of adverse events were excluded from the model. As ustekinumab did not appear to be associated with a greater incidence of adverse events, this was appropriate.

The PBAC accepted that the base case was in the range of $15,000 - $45,000 /extra QALY gained.

The base case of the modelled economic evaluation assumed an initial treatment period of 24 weeks (as a proxy for 28 weeks), the submission appropriately performed a sensitivity analysis assuming only a 16 week (12 week) initiation period.

The results of the univariate sensitivity analyses indicated that the model was sensitive to the maintenance of response rates for etanercept beyond 24 weeks. The results were also sensitive to the assumptions about second- and third-line treatments. The results are fairly sensitive to the costs of best supportive care.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year accounting for market share as necessary was estimated to be less than 10,000 in Year 5 for all biologics.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended listing ustekinumab on the PBS for the treatment of severe chronic plaque psoriasis on the basis of acceptable cost-effectiveness compared with etanercept (50 mg/week). The PBAC agreed that the listing of ustekinumab on the PBS for this condition would offer an alternative therapy with a novel mode of action.

The PBAC agreed that etanercept was the appropriate main comparator, and that adalimumab and infliximab were appropriate secondary comparators. The PBAC noted that comparisons with efalizumab were also provided however they were not considered relevant due to withdrawal of efalizumab from the Australian market.

The PBAC considered the indirect comparison of the ustekinumab (PHOENIX) trials with the etanercept 50 mg/week trials provided the base case for the submission as the etanercept dose is equivalent to the current PBS subsidised dose of etanercept. The result of the indirect comparison for PASI 75 response rates at 12 weeks for the ITT population according to weight and relevant dosage indicated that statistically significantly more patients achieved a PASI 75 response when treated with ustekinumab compared with etanercept 50 mg/week.

The PBAC noted that in the direct randomised (ACCEPT) trial comparing ustekinumab with etanercept 100 mg/week, the etanercept dose used was double the current PBS-subsidised dose of etanercept. However, the results from the ACCEPT trial indicated that statistically significantly more patients achieved a PASI 75 response at 12 weeks when treated with 45 mg or 90 mg ustekinumab compared with etanercept 100 mg/week in the ITT population (not dosed according to weight). An analysis for patients dosed according to the PI recommendations (i.e. ≤ 100 kg 45 mg; > 100 kg 90 mg) demonstrated that statistically significant more patients achieved a PASI 75 response at 12 weeks when:

- Patients weighing ≤ 100 kg were treated with 45 mg ustekinumab; and
- Patients weighing >100 kg were treated with 90 mg ustekinumab. However, for patients weighing > 100 kg treated with 45 mg ustekinumab, ustekinumab is not superior to etanercept.

For patients representative of the PBS eligible population based on failure of previous systemic therapies, a statistically significantly greater proportion of patients achieved a PASI 75 response when treated with 90 mg ustekinumab, but not 45 mg (ITT population, not dosed according to weight).

The PBAC agreed that, based on the supporting data provided in the submission, ustekinumab is more effective and no worse in comparative safety compared with etanercept 50 mg/week at 12 weeks. However, the PBAC did not accept the claim that ustekinumab is more effective and superior in terms of comparative safety than infliximab beyond 24 weeks as no statistical analyses were presented due to asymmetry of available data to confirm this claim. Also assessment of long-term safety data of ustekinumab compared with etanercept and infliximab is unknown as the longest follow-up for safety for infliximab and etanercept is 52 weeks.

The PBAC accepted that the respecified base case was in the range of $15,000 - $45,000 /QALY.

The PBAC noted that the results of the univariate sensitivity analyses indicated that the model was sensitive to the maintenance of response rates for etanercept beyond 24 weeks.

The PBAC noted that the primary outcome of the ustekinumab trials was PASI 75 response at week 12 and that the current initial assessment for a PASI 75 response for PBS-listed biologics was after 12 weeks. However, the PBAC considered it appropriate for the initial treatment period to be 28 weeks with initial assessment of response between weeks 24 and 28

as the base case which was in the range of $15,000 - $45,000 /QALY included the third treatment dose at week 16, with patients receiving treatment at week 0 and week 4 then every 12 weeks thereafter. It was also noted that if assessment was at week 12 patients would only have received 2 doses.

The PBAC advised that patients receiving ustekinumab prior to this recommendation will be grandfathered, and that the grandfather provision should be removed from the listing after 12 months.

Recommendation:
USTEKINUMAB, solution for injection, 45 mg in 0.5 mL

Full details of the restrictions can be viewed at http://www.pbs.gov.au

13. 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.

14. Sponsor's Comment

Janssen-Cilag welcomes this decision by the PBAC to provide access to an additional treatment option for people experiencing severe chronic plaque psoriasis.