JANSSEN-CILAG Ltd

Ustekinumab for treatment of moderate to severe psoriasis

Janssen-Cilag Ltd's Response to Clarification Questions

Following on from your letter dated 28th January 2009, please find below Janssen-Cilag Ltd's responses to the clarification questions on the clinical and cost-effectiveness data contained within our original submission.

Section A: Clarification on effectiveness data

A1. In the Phoenix 1 and 2 trials, the placebo treatment arms divide at 12 weeks. Please clarify if this was a randomised split or if the population was split by some other means.

The placebo arms of the PHOENIX 1 and 2 trials were randomised to either the ustekinumab 45mg or 90mg groups at week 12. Patients were randomly assigned to either group on a 1:1 ratio using a biased-coin minimisation assignment via centralised interactive voice response system. In PHOENIX 1, the investigators were blinded until week 76 whereas in PHOENIX 2, investigators were blinded until week 52.

A2. Table 6.3.1., page 30, does not include the proportion of people in each ustekinumab trial arm who were above and below 100kg. Please provide this information.

The following table shows the percentages of patients in each trial who were above and below 100kg at baseline:

	≤100kg % (n)	**>100kg % (n)**
PHOENIX 1		
Ustekinumab 45mg	65.9% (168/255)	34.1% (87/255)
Ustekinumab 90mg	64.1% (164/256)	35.9% (92/256)
Placebo	65.1% (166/255)	34.9% (89/255)
PHOENIX 2		
Ustekinumab 45mg	72.6% (297/409)	27.4% (112/409)
Ustekinumab 90mg	70.6% (290/411)	29.4% (121/411)
Placebo	70.7% (290/410)	29.3% (120/410)
ACCEPT		
Ustekinumab 45mg	72.2% (151/209)	27.8% (58/209)
Ustekinumab 90mg	70.3% (244/347)	29.7% (103/347)
Etanercept 50mg twice Weekly	72.3% (251/347)	27.7% (96/347)

The percentage of patients who are >100kg is [redacted] in the three clinical trials than the UK specific estimate we have used within the main submission (20%) to estimate the weighted average ICERs for ustekinumab. [redacted]

A3. In section 6.4.1, page 47, the text states that 742 participants were included in the efficacy analysis. However, the corresponding figure suggests all 766 were included. The same issue appears on page 50 for the Phoenix 2 trial. Please clarify which figures were used for the efficacy analyses.

Our apologies for any confusion. We can clarify that the number of patients included in the efficacy analyses for the PHOENIX 1 and PHOENIX 2 trials were 766 and 1,230, respectively. This relates to the intention-to-treat (ITT) population. The text above the table was included incorrectly and was a typographic error.

A4. In Table 6.6.2, page 74, the ustekinumab weight based results across the three trials show the same number of participants for the 45mg and 90mg. Please clarify if this is an error, and if so, please correct the table accordingly.

Thank you for bringing this to our attention. We can clarify that the patient numbers reported for PHOENIX 2 and the ACCEPT trials in Table 6.6.2b have been reported incorrectly. We have provided a corrected table below:

Table 6.6.2b Patient characteristics and main results - baseline severity

	PASI (0-72)	PGA (0-5)	DLQI
Adalimumab			
Gordon 2006	Mean (range) Placebo (n=52): 16 (5.5-40.4) Adalimumab 40mg EOW (n=45):16.7 (5.4-39) Adalimumab 40mg/wk (n=50):14.5 (2.3-42.4)	Moderate to severe psoriasis (%) Placebo (n=52): 29 Adalimumab 40mg EOW (n=45):56 Adalimumab 40mg/wk (n=50):42 Severe psoriasis (%) Placebo (n=52)= 8; adalimumab 40mg EOW(n=45)= 9; adalimumab 40mg/wk (n=50) = 8	NR
Saurat 2007 & Revicki 2008	Mean, SD (range) Placebo (n=53): 19.2, 6.9 (6.5-38.1) methotrexate (n=110): 19.4,7.4 (9.3-46.6) adalimumab (n=108) : 20.2, 7.5 (10.4-52.9)	Very severe psoriasis (%) Placebo (n=53): 3.8 methotrexate (n=110): 5.5 adalimumab (n=108):8.4 Moderate to severe psoriasis (%) Placebo (n=53): 58.5	NR

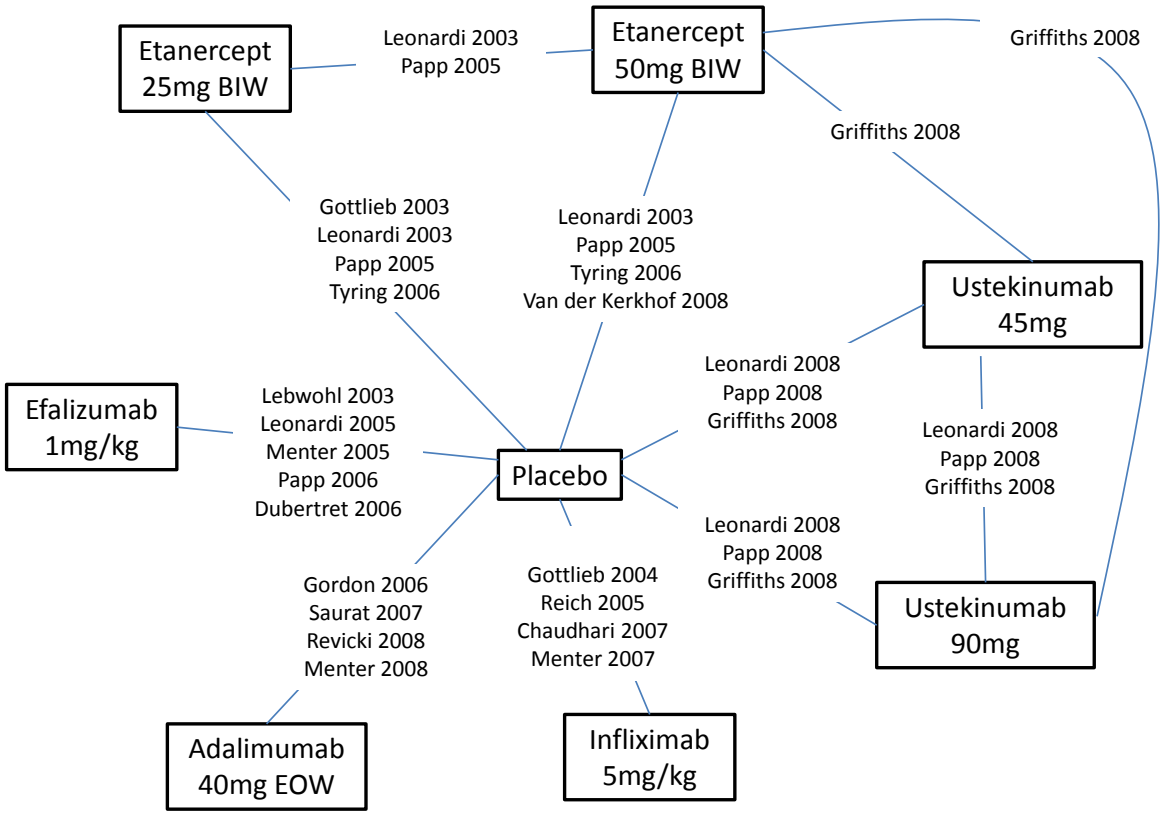
		Methotrexate (n=110): 41.8 adalimumab (n=108) :43 Moderate psoriasis (%) Placebo (n=53): 37.7 methotrexate (n=110): 52.7 adalimumab (n=108): 47.7	
Menter 2008	Mean (SD) Placebo (n=398): 18.8 (7.09) Adalimumab (n=814): 19 (7.08)	Moderate, n (%) Placebo (n=398): 220(55.3) Adalimumab (n=814): 417(51.2) Severe, n (%) Placebo (n=398): 155(38.9) Adalimumab (n=814): 346 (42.5) Very Severe, n (%) Placebo (n=398): 23(5.8) Adalimumab (n=814): 51(6.3)	NR
Efalizumab			
Dubertret 2006	Mean, SD Placebo (n=264): 23, 9.6 Efalizumab (n=529):23.6, 20.2	Mild, n (%) Placebo (n=264): 9 (3.4) Efalizumab (n=529):13 (2.5) Moderate, n (%) Placebo (n=264): 137 (51.9) Efalizumab (n=529): 275 (52) Severe, n (%) Placebo (n=264): 108 (40.9) Efalizumab (n=529): 221 (41.8) Very Severe, n (%) Placebo (n=264): 10 (3.8) Efalizumab (n=529)= 20 (3.8)	NR
Lebwohl 2003	Total study population n=597 The mean baseline psoriasis area and severity index was 20.	NR	NR
Leonardi 2005	Mean (range) Placebo (n=170): 19(9.6-57.6) Efalizumab 1mg/kg/wk (n=162):18.6 (11.9-50.1) Efalizumab 2mg/kg/wk (n=166):18.9 (10-55.6)	NR	NR
Menter 2005	Mean (range) Placebo (n=187): 19.4 (11.4-50.3) Efalizumab (n=369):19.4 (10.1-58.7)		
Papp 2006	Mean (SD) Placebo (n=236): 18.69,7 (10.5-49.6) Efalizumab (n=450): 19.14,7.5 (10.2 – 54.6)	Mild, n (%) Placebo (n=236): 15 (6.4) Efalizumab (n=450): 20 (4.5) Moderate, n (%) Placebo (n=236): 131 (55.5); Efalizumab (n=450): 253 (56.3) Severe, n (%) Placebo (n=236): 82 (34.7); Efalizumab (n=450): 156 (34.7) Very Severe, n (%) Placebo (n=236): 8 (3.4); Efalizumab (n=450): 20 (4.5)	NR
Etanercept			
Gottlieb 2003	Mean (SE) Placebo (n=55): 19.5 (1.3) Etanercept 25mg BIW (n=57): 17.8 (1.1)	*NR*	NR
Leonardi 2003	Mean (SE) Placebo (n=166): 18.3 (0.6); Etanercept 25mg QW (n=160): 18.2 (0.7) Etanercept 25mg BIW (n=162): 18.5 (0.7) Etanercept 50mg BIW (n=164): 18.4 (0.7)	Marked or Severe (%) Placebo (n=166): 23 Etanercept 25mg QW (n=160): 21 Etanercept 25mg BIW (n=162): 23 Etanercept 50mg BIW (n=164): 21	Mean (SE) Placebo (n=166): 12.8 (0.6) Etanercept 25mg QW (n=160):12.2 (0.5) Etanercept 25mg BIW (n=162):12.7

			(0.5) Etanercept 50mg BIW (n=164):11.3 (0.5)
Papp 2005	Median (range) Placebo (n=193): 16 (7-62.4) Etanercept 25mg BIW (n=196): 16.9 (4-51.2) Etanercept 50mg BIW (n=194): 16.1 (7-57.3)	NR	NR
Tying 2006	Mean (SD) Placebo (n=307): 18.1 (7.4) Etanercept 50mg BIW (n=311): 18.3 (7.6)	NR	Mean (SD) Placebo (n=307): 12.5 (6.7) Etanercept 50mg BIW (n=311):12.1(6.7)
Infliximab			
Chaudhari 2001	Mean (SD), range Placebo (n=11): 20.3 (5.5), 13.8-31.9 Infliximab 5mg/kg (n=11): 22.1(11.5),10-42.6 Infliximab 10mg/kg (n=11): 26.6 (10.3), 14.8-42	NR	NR
Gottlieb 2004	Median (IQR) Placebo (n=51): 18, (15,27) Infliximab 3mg/kg (n=99): 20 (15,26) Infliximab 5mg/kg (n=99): 20 (14,28)	NR	Median (IQR) Placebo (n=51): 14, (9,18) Infliximab 3mg/kg (n=99): 11 (6,17), Infliximab 5mg/kg (n=99): 12 (8,17)
Menter 2007	Mean (SD), median Placebo (n=208): 19.8 (7.7), 17.4 Infliximab 3mg/kg (n=313): 20.1(7.9), 17.6 Infliximab 5mg/kg (n=314): 20.4 (7.5), 18.6	NR	Mean (SD), median Placebo (n=208): 13.4 (7.3), 13 Infliximab 3mg/kg (n=313):12.8(6.9), 12 Infliximab 5mg/kg (n=314):13.1 (7.0), 12.5
Reich 2005	Mean (SD) Placebo (n=77): 22.8 (8.7) Infliximab (n=301): 22.9 (9.3)	NR	NR
Ustekinumab			
Leonardi 2008 (PHOENIX 1) ITT	Mean (SD) Placebo (n=255): 20.4 (8.6) Ustekinumab 45mg (n=255): 20.5 (8.6) Ustekinumab 90mg (n=256): 19.7 (7.6)	Marked or severe, n (%) Placebo (n=255):112 (43.9) Ustekinumab 45mg (n=255):114 (44.7) Ustekinumab 90mg (n=256):109 (42.6)	Mean (SD) Placebo (n=255) = 11.8 (7.4); Ustekinumab 45mg (n=255) = 11.1 (7.1) Ustekinumab 90mg (n=256) = 11.6 (6.9)
PHOENIX 1 Weight based	Mean (SD) Ustekinumab 45mg (n=168) 19.9 (8.3) Ustekinumab 90mg (n=92) 20.6 (7.9)		Mean (SD) Ustekinumab 45mg (n=168) 10.9 (6.9) Ustekinumab 90mg (n=92) 11.6 (7.2)
Papp 2008 (PHOENIX 2) ITT	Mean (SD) Placebo (n=410): 19.4 (7.5) Ustekinumab 45mg (n= 409):19.4 (6.8) Ustekinumab 90mg (n= 411):20.1 (7.5)	Marked or severe, n (%) Placebo (n=410): 160 (39) Ustekinumab 45mg (n= 409): 169 (41.3) Ustekinumab 90mg (n= 411): 159 (38.7)	Mean (SD) Placebo (n=410): 12.3 (6.9) Ustekinumab 45mg (n= 409):12.2 (7.1) Ustekinumab 90mg (n= 411): 12.6 (7.3)

PHOENIX 2 Weight based	Mean (SD) Ustekinumab 45mg (n=297) 19.6 (7.2) Ustekinumab 90mg (n=121) 21.2 (7.9)		Mean (SD) Ustekinumab 45mg (n=297) 12.4 (7.1) Ustekinumab 90mg (n=121) 13.4 (7.9)
Griffiths 2008 (ACCEPT) ITT	Mean, SD (range) Etanercept (n=347): 18.64 (6.1); Ustekinumab 45mg (n= 209): 20.49 (9.1) Ustekinumab 90mg (n= 347): 19.87 (8.3)	Moderate, n (%) Etanercept (n=347): 199 (57.3) Ustekinumab 45mg (n= 209) 111(53.1) Ustekinumab 90mg (n= 347): 201 (58.1) Marked, n (%) Etanercept (n=347): 135 (38.9) Ustekinumab 45mg (n= 209): 87 (41.6) Ustekinumab 90mg (n= 347): 135 (39) Severe, n (%) Etanercept (n=347): 13 (3.7) Ustekinumab 45mg (n= 209): 11 (5.3) Ustekinumab 90mg (n= 347): 9 (2.6)	NR
ACCEPT Weight based	Mean (SD) Ustekinumab 45mg (n=151) 20.5 (9.1) Ustekinumab 90mg (n=103) 21.4 (9.6)		Not applicable

A5. Please provide a network diagram for the mixed treatment comparison (MTC)

Below is a network diagram for the mixed treatment comparison:



This excludes all comparisons which have not been included in the meta-analysis and would not have added to the network, for example the adalimumab comparison versus methotrexate in the CHAMPION trial (Saurat 2007).

A6. We note that a subgroup will be recommended in the SPC. Please provide details of the analysis for this sub-group, the results of which are used in the MTC and the economic model. In particular, please provide a description of the method used which justified the cut-off weight of 100kg for the use of a higher dose of ustekinumab.

The PASI 75 response rate at week 12 for both doses of ustekinumab were analysed for each 10kg increment of patient weight in a pooled analysis of PHOENIX 1 and PHOENIX 2. In this pooled analysis, the response rates for the 45mg and 90mg doses were comparable for each 10kg increment of patient weight below the 100kg cut-off. However, for patients weighing >100kg, there was a greater difference in

efficacy between the 45mg and 90mg groups (see figure 7.2.1 in the original submission document).

The dose/response relationship for ustekinumab observed at the 100kg cut-off in the PHOENIX 1 and PHOENIX 2 trials has been further confirmed by pharmacokinetic research published in February 2009 (Zhu et al, 2009[1]). In pharmacokinetic modelling of the apparent clearance (CL/F) and apparent volume of distribution (V/F) of ustekinumab, Monte Carlo simulation indicated that the mean steady-state trough serum concentration of ustekinumab with every-12-week dosing for patients weighing more than 100kg was approximately 30% lower than for patients weighing 100kg or less.

Finally, based on the dose/response relationship observed in the PHOENIX 1 and PHOENIX 2 trials, the Phase III ACCEPT trial was designed with weight-based efficacy as a major secondary endpoint. In this analysis, the combined ustekinumab group (weight-based) was composed of subjects randomised to ustekinumab 45mg and with baseline weight ≤100kg and those randomised to ustekinumab 90mg and with baseline weight >100kg.

A7. On page 109, the submission indicated that it has been demonstrated that the response rate for ustekinumab continues to rise after 12 weeks and therefore the assumption that the response at 16 weeks is the same as 12 weeks is justified. This statement is not referenced back to another section of text in the submission. Please clarify which section of the submission you are referring to.

The longer term efficacy of ustekinumab has been demonstrated in the PHOENIX trials and can be seen in section 6.4.5. However, 12 weeks was the final randomised comparison to placebo and therefore we have assumed equal efficacy with this time point. To further illustrate the longer term efficacy of ustekinumab, the percentage of patients achieving a PASI 75 at various time points up to week 28 are shown in the table below:

[1] Zhu et al. Population pharmacokinetic modelling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40 in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol* 2009; 49; 162

	PHOENIX 1 (weight based analysis*)		PHOENIX 2 (weight based analysis*)	
% PASI 75	Ustekinumab 45mg	Ustekinumab 90mg	Ustekinumab 45mg	Ustekinumab 90mg
at Week 4	10.7%	9.8%	20.9%	11.6%
at Week 8	61.3%	45.6%	62.0%	58.8%
at Week 12	73.8%	68.5%	73.4%	71.1%
at Week 16	73.8%	67.8%	76.0%	68.1%
at Week 20	80.1%	80.0%	80.6%	78.4%
at Week 24	82.5%	80.0%	80.1%	79.8%
at Week 28	79.3%	74.4%	75.6%	73.9%

* Ustekinumab 45mg for patients ≤100kg and ustekinumab 90mg for patients >100kg

Section B: Clarification on cost-effectiveness data

B1. Please clarify the number of references/studies deemed appropriate for critical appraisal in the cost-effectiveness literature search. The numbers in 7.1.1 (overview of literature review results, page 93) do not appear to add up.

Thank you again for drawing this to our attention. We can clarify that overall, six references were identified for potential inclusion into the review (Woolacott et al. 2006, Pearce et al. 2006, CADTH 2007, Nelson et al, 2008, Menter & Baker 2005 and Hankin et al. 2005). Of these, two were deemed to be appropriate for data extraction and full appraisal (Woolacott et al. 2006 and Pearce et al. 2006). One further reference provided an overview of all other studies (CADTH 2007), and the remaining three studies were considered to not be of high quality based on their basic methodological flaws and simple modelling approach and were not deemed useful enough from a methodological and outcome point of view to warrant full critical appraisal (Menter & Baker 2005, Hankin et al. 2005 and Nelson et al. 2005).

B2. Please provide the source for the range of the efficacy variable for intermittent etanercept used in the sensitivity analysis in Table 7.2.13, page 125.

No measure of uncertainty or other criteria was available to inform this decision and as such a total range of 20% was considered appropriate to assess the sensitivity to plausible uncertainty in this parameter. It should be noted that subsequent to publication a further study (Ortonne et al, 2008[2]) has addressed the question of the efficacy of intermittent etanercept and has shown consistent results with Moore et al, 2008 where intermittent etanercept is significantly less effective than continuous

[2] Ortonne J-P et al. Efficacy and safety of continuous versus paused etanercept treatment in patients with moderate-to-severe psoriasis over 54 weeks: the CRYSTEL study. *Expert Rev. Dermatol.* 3(6), 657-665 (2008)

etanercept treatment. This study involved patients with moderate to severe plaque psoriasis who were randomised to receive continuous etanercept 25mg twice weekly or 'paused' etanercept for 54 weeks. Among 711 patients evaluable for efficacy, the mean PGA score averaged over 54 weeks (primary endpoint) was significantly lower in the continuous etanercept group than in the 'paused' etanercept group (1.98 vs. 2.51, respectively; p<0.001). Mean PGA was significantly reduced from baseline (3.6, both groups) to week 54 in the continuous (1.9) and paused groups (2.4; p<0.01). Mean PASI was significantly decreased from baseline (21.9 and 22.8, respectively) to week 54 with continuous (7.1) and paused therapy (9.5; p<0.01). PASI improved by 68% and 59% from baseline to week 54 in patients receiving continuous and paused etanercept, respectively.

B3. Please provide an additional economic analysis that does not incorporate the patient access scheme.

Below is the weighted average base case analysis for ustekinumab without the patient access scheme.

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£40,952	-
Efalizumab	£5,264	0.1308	£44,597	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£102,034	£30,111
Etanercept 25mg continuous	£4,829	0.1409	£103,157	£34,281
Etanercept 50mg	£5,333	0.1483	£137,323	£35,964
Adalimumab	£4,660	0.1502	£300,063	£31,022
Ustekinumab	£6,387	0.1560	-	£40,952
Infliximab	£6,327	0.1616	Dominated	£39,153

Please note: the weighted average has been estimated where 80% of patients are≤100kg and receive ustekinumab 45mg and the remaining 20% of patients are >100kg and receive ustekinumab 90mg.

In addition, please find below the weight by dose for ustekinumab deterministic analysis excluding the patient access scheme.

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab 45mg vs other treatments	ICER Ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£29,334	£88,417	-
Efalizumab	£5,264	0.1308	Dominant	£357,606	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£25,035	£444,131	£30,111
Etanercept 25mg continuous	£4,829	0.1409	Dominant	£661,382	£34,281
Etanercept 50mg	£5,333	0.1483	Dominant	£1,411,694	£35,964
Adalimumab	£4,660	0.1502	Dominant	£2,266,322	£31,022
Ustekinumab 90mg	£13,631	0.1542	Dominant	-	£88,417
Ustekinumab 45mg	£4,588	0.1564	-	Dominated	£29,334
Infliximab	£6,327	0.1616	£334,423	Dominated	£39,153

B4. Please provide an economic analysis that uses a 28-week stopping rule for the trial period, as per the guidance given in the SPC.

Per the recommendation in the ustekinumab SPC that consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment, we have run a cost-effectiveness analysis using a 28-week stopping rule for ustekinumab. [redacted], but with the 28-week stopping rule, assumes that there are 3 doses of ustekinumab used during the 28-week trial period (week 0, 4, and 16) as opposed to 2 doses used in the base case trial period of 16 weeks. Both costs and utilities have been adjusted for the 28-week stopping rule in the results tables shown below.

We are presenting two analyses with varying assumptions to estimate the cost-effectiveness of ustekinumab with a 28-week trial period:

Analysis One

We have applied week 28 PASI responses for all patients who were randomised to receive ustekinumab (either dose) at baseline from the PHOENIX trials instead of the mixed treatment comparison (for ustekinumab alone). This has been carried out for the following reasons:

- Patients who were randomised to ustekinumab 45mg or 90mg at week 0 were included in the analysis.
- There is no placebo comparison beyond 12 weeks within the clinical trials. As such, response rates from the mixed treatment comparison cannot be calculated

beyond 12 weeks, because the mixed treatment comparison is dependent on placebo as the common comparator for all agents.

- The database lock for the ACCEPT trial up to 28 weeks has not yet been completed.

Below are the cost-effectiveness results from this analysis:

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£31,533	-
Efalizumab	£5,264	0.1308	Dominant	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£38,944	£30,111
Etanercept 25mg continuous	£4,829	0.1409	£8,781	£34,281
Etanercept 50mg	£5,333	0.1483	Dominant	£35,964
Adalimumab	£4,660	0.1502	£41,548	£31,022
Ustekinumab	£4,978	0.1579	-	£31,533
Infliximab	£6,327	0.1616	£364,595	£39,153

In this analysis, ustekinumab dominates both etanercept 50mg twice weekly and efalizumab. When compared against the most commonly used biologic in the UK, continuous etanercept 25mg twice-weekly, the ICER is £8,781. When compared against adalimumab and intermittent etanercept 25mg twice weekly, the ICERs have increased to £41,548 and £38,944, respectively.

Versus supportive care, the ICER for ustekinumab is £31,533 compared to £29,587 in the original base case analysis presented in section 7.3.1.1 in our submission. This suggests that when comparing against supportive care, the duration of the trial period has a relatively modest impact on the ICER.

The limitation of the analysis provided above relates to the lack of placebo control at the 28 week time point for ustekinumab, however placebo response up to 12 weeks was low and given the severe treatment refractory population enrolled into the studies it is unlikely that this placebo response would have increased greatly with no additional treatment.

Analysis Two

We are also presenting a cost-effectiveness analysis which assumes that all biologics have a 28 week trial period. This assumes that the response rate at the end of the original trial period is maintained at 28 weeks for all treatments. The results are as follows:

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£32,662	-
Efalizumab	£6,070	0.1056	Dominant	£57,497
Etanercept 25mg intermittent	£4,883	0.1127	£4,259	£43,331
Etanercept 25mg continuous	£5,598	0.1198	Dominant	£46,712
Etanercept 50mg	£5,878	0.1309	Dominant	£44,903
Adalimumab	£5,270	0.1476	Dominant	£35,706
Ustekinumab	£5,063	0.1550	-	£32,662
Infliximab	£7,070	0.1440	Dominant	£49,106

In this analysis, ustekinumab dominates adalimumab, efalizumab, continuous etanercept 25mg and 50mg twice weekly and infliximab. When compared to intermittent etanercept 25mg twice weekly, the ICER is low at £4,259. Similar to the previous analysis, the comparison (ICER) against supportive care has not altered significantly despite applying the less favourable 12 week efficacy in place of the 28 week efficacy described above.

B5. [redacted]

[redacted]

B6. Please clarify the assumption that all patients will be able to self-inject. If there is a proportion of patients that are unable to self-inject, please provide an estimate of this proportion.

Each patient will be trained to self-inject. This training will be provided by Janssen-Cilag Ltd. In addition, Janssen-Cilag Ltd is funding (via a third party) nurses to visit patients in their homes to assist with administering the injections if necessary. The costs of providing this service are met fully by Janssen-Cilag Ltd, and we would be happy to provide more details on this if that would be helpful.

B7. Appendix 11 does not appear to contain any methodological details. Given the role that the outcomes of this meeting played in deriving assumptions used in the model, please provide further information on the nature of the advisory board and the way the information was obtained.

The advisory board was externally moderated by SJK Consulting Ltd and included dermatologists and dermatology pharmacists. The information was presented to the group via a PowerPoint presentation (slides are detailed in Appendix 11 of the original submission). This began with an overview of the design of the cost-effectiveness model and then followed with details of each variable including the source information and also Janssen-Cilag Ltd's proposal for each variable estimate. Each was extensively discussed, and a consensus was obtained on each variable.

Section C: Textural clarifications and additional points

C1. Please provide a copy of the draft or final CHMP EPAR

The final CHMP EPAR is attached to this document.

C2. Please provide a list of abbreviations (for example it is unclear what eCRF, CNTO stand for).

See attached document for a full list of abbreviations.

C3. In section 6.9.1, the text is obliterated by the table 6.9. Please replicate the paragraph that cannot be seen on page 89.

We apologise for this formatting issue. The paragraph which appears on page 89 is as follows with referencing as per the original submission:

Etanercept 50mg twice weekly

Twice-weekly doses of etanercept 50mg were used as the active control in the head to head ACCEPT trial of ustekinumab versus etanercept. Although this etanercept dosing regimen has not received a positive recommendation from NICE (TA103)(22) (because, although more effective than 25mg dosing it was not considered to be cost-effective), it is licensed in England & Wales for the treatment of moderate to severe psoriasis. Etanercept 50mg twice weekly dosing for the first 12 weeks is the maximum approved dose and schedule for the drug, and provides a reasonable timeframe for comparison of the initial efficacy of ustekinumab versus etanercept. To evaluate whether ustekinumab represented a significant therapeutic advance in the treatment of patients with moderate to severe plaque psoriasis, comparing the ustekinumab benefit-risk profile against the highest approved dose and schedule of etanercept was thought to provide the fairest basis of comparison. Additionally, there is current evidence from database studies that demonstrates that this higher dose is still being used in the UK(67) (see Appendix 6). Therefore, this is an appropriate comparator for ustekinumab in relation to the decision problem.

11th February 2009

JANSSEN-CILAG Ltd

Ustekinumab for treatment of moderate to severe psoriasis

Calculation of the efficacy associated with etanercept 25mg intermittent

We have identified a minor error in the way in which the efficacy adjustment has been made for etanercept 25mg intermittent in our original submission. As a result we have updated the relevant text from the submission including the cost-effectiveness analyses. The updated text can be seen below with the changes highlighted in red. Overall, the impact of this change is minimal.

7.2.6.1 Framework (Extract)

As described in section 7.2.7.3 of this report, utility for patients who reach a PASI 75 during the 'trial' period and continue into long term dosing is estimated from the proportion of patients at a PASI 90 and the proportion between PASI 75 and 90 after the initial 'trial' period (estimated from the mixed treatment meta-analysis). This is applied to the utility values associated with each of these PASI response levels. That is to say that on continuous dosing, those who achieve PASI 75 in the 'trial' period, and do not drop out subsequently, are assumed to maintain the clinical response they achieved during the 'trial' period. To allow for a reduction in efficacy on intermittent dosing we have relaxed that assumption and assumed that a proportion of those achieving a PASI 90 will have their response fall to PASI 75-90, whilst a proportion of those achieving a PASI 75-90 will fall to a PASI 50-75 (see Figure 7.2.2). No data was available to provide direct evidence of those proportions, however the study by Moore *et al* (2007) does provide data that we have used as a proxy. In that study after 12 weeks of intermittent dosing 69% of those patients who had originally responded to an induction course of etanercept continued to respond (as measured by a PGA of ≤2), compared to 85% amongst those dosing continuously. We, therefore, used the ratio of these two values as our adjustment factor for the proportion of patients failing to maintain their original PASI response, so in the base case we assumed that 81.5% of patients would maintain their original response whilst 18.5% would fall by one level. This estimate has been subjected to sensitivity analyses.

7.3.1.1 What were the results of the base-case analysis?

Deterministic analysis

Weight by dose for ustekinumab - weighted average analysis

The results from the base case analysis are shown in table 7.3.1. Overall, the weighted average estimate for ustekinumab generates more QALYs than all other treatment options with the exception of infliximab. The weighted average has been estimated as 80% of patients receive ustekinumab 45mg (patients ≤100kg) and 20% receive ustekinumab 90mg (patients >100kg) (See Appendix 6). Apart from supportive care, etanercept 25mg intermittent produces the lowest QALY gains. In terms of cost, etanercept 25mg intermittent has the lowest mean costs. Ustekinumab is cheaper on average than adalimumab, efalizumab, etanercept 25mg and 50mg

continuous and infliximab. The ICER for ustekinumab versus supportive care is estimated to be £29,587. Furthermore the ICER is estimated to be £27,105 for ustekinumab versus etanercept 25mg intermittent, whereas ustekinumab dominates all other treatments with the exception of infliximab.

Table 7.3.1 Base case results (weighted average - weight by dose for ustekinumab) - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab vs other treatments	ICER vs supportive care
Supportive care	0.0000	£0	£29,587	-
Efalizumab	0.1308	£5,264	Dominant	£40,250
Etanercept 25mg intermittent	0.1329	£3,989	£27,105	£30,019
Etanercept 25mg continuous	0.1409	£4,829	Dominant	£34,281
Etanercept 50mg continuous	0.1483	£5,333	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£31,022
Ustekinumab	**0.1560**	**£4,615**	**-**	£29,587
Infliximab	0.1616	£6,327	*£304,566	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for willingness to pay thresholds up to £30,000 ustekinumab is the favoured option over infliximab

Based on the results presented in table 7.3.1, comparing against the current standard of care which is etanercept 25mg intermittent results in ustekinumab dominating all other biologic interventions with infliximab being rendered not cost-effective compared with ustekinumab (see table 7.3.2 and figure 7.3.2).

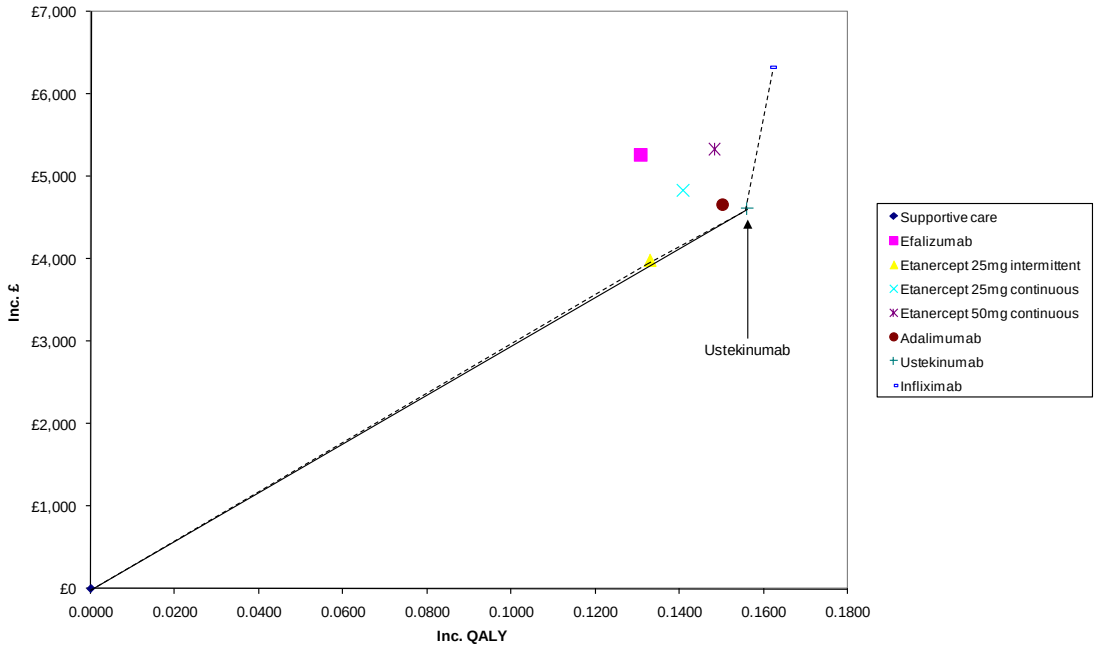
Table 7.3.2 Analysis comparing against the current standard of care etanercept 25mg intermittent

Treatment	Mean QALYs	Mean costs	ICER vs next cost-effective treatments	
Supportive care	0.0000	£0	-	
Efalizumab	0.1308	£5,264	£40,250	
Etanercept 25mg intermittent	0.1329	£3,989	£30,019	*Extended dominated by ustekinumab*
Etanercept 25mg continuous	0.1409	£4,829	£105,098	Dominated by ustekinumab
Etanercept 50mg continuous	0.1483	£5,333	£67,865	Dominated by ustekinumab
Adalimumab	0.1502	£4,660	£38,707	Dominated by ustekinumab
Ustekinumab	0.1560	£4,615	£27,105	
Infliximab	0.1616	£6,327	£304,566	

In table 7.3.2 each comparator is presented in successive rows ordered by the number of QALYs generated. Each option is then compared to the next best option with lower cost. Options shown in italics are considered dominated by a subsequent option and hence may be excluded from decision-making. In addition etanercept intermittent is seen to be extended dominated by ustekinumab and is thus also excluded from the decision.

These results are also displayed in figure 7.3.2 below from which we can see that ustekinumab dominates all treatment options except etanercept 25mg intermittent versus which it displays extended dominance (ustekinumab has higher effectiveness and costs).

Figure 7.3.2 Cost-effectiveness plane



Probabilistic analysis

The table 7.3.3 below presents the same information as in table 7.3.1, derived from the mean costs and effects across 10,000 Monte Carlo simulations conducted for the probabilistic sensitivity analysis.

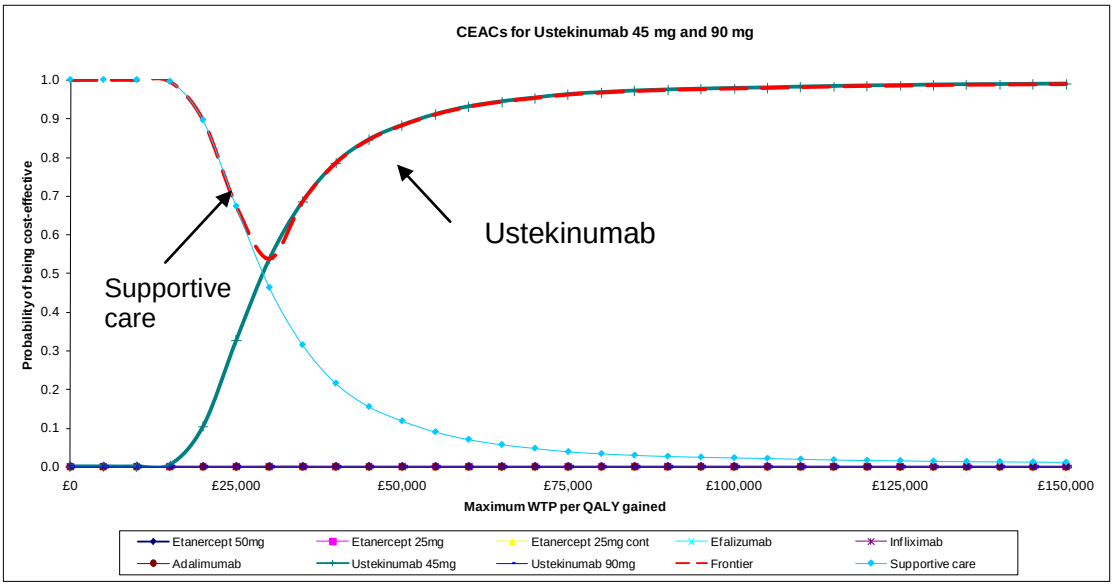
Table 7.3.3 Base case results (weighted average - weight by dose for ustekinumab) - probalistic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab vs other treatments	ICER vs supportive care
Supportive care	0.0000	£0	£29,127	-
Efalizumab	0.1307	£5,299	Dominant	£40,528
Etanercept 25mg intermittent	0.1336	£3,968	£25,842	£29,708
Etanercept 25mg continuous	0.1416	£4,810	Dominant	£33,971
Etanercept 50mg continuous	0.1472	£5,495	Dominant	£37,325
Adalimumab	0.1526	£4,536	9,195	£29,730
Ustekinumab	**0.1572**	**£4,579**	**-**	£29,127
Infliximab	0.1616	£6,363	£402,186	£39,369

* this ICER compares infliximab to ustekinumab. Therefore, for all willingness to pay thresholds of less than this would result in the favouring of ustekinumab over infliximab

Figure 7.3.2 shows the cost-effectiveness acceptability curve resulting from the probabilistic sensitivity analysis. Of the biologic agents, ustekinumab has the highest probability of being cost-effective at conventional NICE thresholds.

Figure 7.3.2 Cost-effectiveness acceptability curves for biologics in the base case (weighted average - weight by dose for ustekinumab)



At the £20,000 and £30,000 willingness to pay thresholds, ustekinumab is the only biologic that is likely to be cost-effective. All other biologics have a zero probability of being cost-effective.

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

Scenario one: Weight based dosing for ustekinumab (ustekinumab 45mg for ≤100kg and ustekinumab 90mg for >100kg)

The results for the weight based dosing analysis are shown in Figure 7.3.5. Overall, when applying weight based dosing ustekinumab when compared to supportive care results in an incremental cost-effectiveness ratio of £29,334 for ustekinumab 45mg and £30,693 for ustekinumab 90mg.

When compared to the other biologic agents, ustekinumab 45mg dominates all other treatment options, apart from etanercept 25mg intermittent where the ICER is estimated to be £25,468 and infliximab. Ustekinumab 90mg has an ICER of £34,897 when compared to etanercept 25mg intermittent and it dominates all other biologic agents with the exception of adalimumab, infliximab and ustekinumab 45mg, however clearly these are two doses of ustekinumab are not alternatives for the same patients.

Table 7.3.5 Weight based dosing for ustekinumab - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab 45mg vs other treatments	ICER ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	0.0000	£0	£29,334	-	-
Efalizumab	0.1308	£5,264	Dominant	Dominant	£40,250
Etanercept 25mg intermittent	0.1329	£3,989	£25,468	£34,897	£30,019
Etanercept 25mg continuous	0.1409	£4,829	Dominant	Dominant	£34,281
Etanercept 50mg continuous	0.1483	£5,333	Dominant	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£18,204	£31,022
Ustekinumab 45mg	**0.1564**	**£4,588**	**-**	**Dominated**	**£29,334**
Ustekinumab 90mg	**0.1542**	**£4,732**	**Dominant**	**-**	**£30,693**
Infliximab	0.1616	£6,327	£334,205	-	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for conventional willingness to pay thresholds,ustekinumab is favoured over infliximab

Scenario two: All patients analysis

The cost-effectiveness results for the all patients analysis (i.e. no weight based dosing for ustekinumab) are shown in table 7.3.6 below.

Table 7.3.6 All patients analysis for ustekinumab - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab 45mg vs other treatments	ICER ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	0.0000	£0	£30,664	-	-
Efalizumab	0.1311	£5,252	Dominant	Dominant	£40,052
Etanercept 25mg intermittent	0.1334	£3,960	£36,983	£28,633	£29,671
Etanercept 25mg continuous	0.1415	£4,802	Dominant	Dominant	£33,930
Etanercept 50mg continuous	0.1484	£5,352	Dominant	Dominant	£36,061
Adalimumab	0.1504	£4,669	16,400	Dominant	£31,046
Ustekinumab 45mg	**0.1544**	**£4,735**	**-**	**Dominant**	**£30,664**
Ustekinumab 90mg	**0.1563**	**£4,613**	**Dominated**	**-**	**£29,520**
Infliximab	0.1617	£6,342	£221,386	-	£39,227

* this ICER compares infliximab to ustekinumab. Therefore, for conventional willingness to pay thresholds,ustekinumab is favoured over infliximab

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

Extensive sensitivity analyses have been carried out on the base case and the results from the univariate sensitivity analysis for both 45mg and 95mg can be seen in Table 7.3.6 below.

Overall, the model is sensitive to the following:

The number of hospital days associated with supportive care - with ICERs versus etanercept 25mg intermittent ranging from ustekinumab £20,672 to £34,387 when 27.5 and 17.5 days hospitalisation are assumed respectively. Overall, ustekinumab dominates all other biologics other than etanercept 25mg intermittent and infliximab, and the latter is rendered not to be cost-effective in the presence of ustekinumab.

Estimate of the cost of dosing for intermittent etanercept 25mg – the ICERs range from ustekinumab dominating etanercept 25mg intermittent at the 98% level to £69,442 when using the 74% as was used in TA103. Database evidence suggests now that there is only one day between use of intermittent etanercept per year or 98% of the continuous cost (See Appendix 6).

Use of SF-6D utility scores – The ICERs versus supportive care of £49,371 compared the base case of £29,587. However, this is not entirely unexpected based on the concerns raised earlier about the sensitivity of this instrument across the range of utility values seen in this condition. Further support is given to the inappropriateness of this approach by the values generated by the direct mapping from PASI undertaken by the manufacturer of adalimumab for their successful submission TA146. This mapping also suggests a stronger gradient between PASI response and utility than suggested by the SF-6D mapping.

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Table 7.3.6 Results from the univariate sensitivity analysis for ustekinumab

Ustekinumab versus	Value	Supportive care	Adalimumab	Efalizumab	Etanercept 25mg intermittent	Etanercept 25mg cont	Etanercept 50mg cont	Infliximab
Length of stay	17.5	£34,387	Dominant	Dominant	£34,812	Dominant	Dominant	-
	27.5	£20,672	Dominant	Dominant	£21,117	Dominant	Dominant	-
Drop-out rate	10%	£26,552	Dominant	Dominant	£34,807	Dominant	Dominant	-
	30%	£33,488	Dominant	Dominant	£20,570	Dominant	Dominant	-
Duration of initial period	12 weeks	£29,919	Dominant	Dominant	£29,349	Dominant	Dominant	-
Estimate of cost dose for etanercept intermittent	74% of cont dose	£29,587	Dominant	Dominant	£69,542	Dominant	Dominant	-
	98% of cont dose	£29,587	Dominant	Dominant	Dominant	Dominant	Dominant	-
SF-36-SF6D	See table 7.2.13	£49,371	Dominant	Dominant	£30,558	Dominant	Dominant	-
EQ-5D based on mapping from PASI	See table 7.2.13	£29,302	Dominant	Dominant	£15,513	Dominant	Dominant	-
EQ-5D based on mapping from DLQI – German utility study	See table 7.2.13	£29,637	Dominant	Dominant	£27,072	Dominant	Dominant	-
Percentage of patients >100kg	6%	£29,409	Dominant	Dominant	£25,948	Dominant	Dominant	-
	17%	£29,549	Dominant	Dominant	£26,853	Dominant	Dominant	-
Discount rate	0%	£28,634	Dominant	Dominant	£28,998	Dominant	Dominant	-
	6%	£30,272	Dominant	Dominant	£25,755	Dominant	Dominant	-
Efficacy of intermittent etanercept 25mg (% of continuous use)	71%	£29,587	Dominant	Dominant	£22,634	Dominant	Dominant	-
	91%	£29,587	Dominant	Dominant	£32,949	Dominant	Dominant	-

- refers to a comparison where the comparator has greater benefits but also at a greater cost
Dominant refers to ustekinumab dominating the specified treatment option

Appendix: Patient Access Scheme

Background

This scheme has been developed to ensure that patients who weigh 100kg or more are able to equitably access Stelara®.

Situational Analysis - Stelara® – weight based dosing

Stelara® (Ustekinumab) will be available at launch as a 45mg vial for sub-cutaneous injection. The SmPC recommends that the dose is 90mg for people who are >100kg in weight, which will have to be administered in the form of 2*45mg vials until such time that other formulations become commercially available.

The posology in the SmPC is as follows: *Adults (18-64 years) with moderate to severe psoriasis. The recommended dose is an initial dose of 45 mg administered subcutaneously at week 0 followed by a 45 mg dose at week 4, then every 12 weeks thereafter. For patients with a body weight >100kg the dose is 90mg, administered subcutaneously at week 0 followed by a 90 mg dose at week 4, then every 12 weeks thereafter. In patients weighing >100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients.*

Our objective is to seek a mechanism to secure cost-effective access for all patients.

Patient Access Scheme

To address this challenge we are proposing a scheme that applies only to those patients who are over 100kg and may require 90mg dosing. Therefore, under the terms of the patient access scheme that has been agreed with the Department of Health and approved by Ministers, patients who are over 100kg in weight and who are prescribed the 90mg (2x45mg) dose will receive both vials at a total cost of £2,147. This access scheme will be available to the NHS upon registration of the patient with Janssen-Cilag Ltd. Janssen-Cilag Ltd will offer the benefits of the patient access scheme at least until any re-review of the guidance by NICE or the introductions of any new formulations that would render the scheme obsolete. Janssen-Cilag Ltd will not withdraw the scheme without prior agreement with NICE and the Department of Health.

This scheme would be administered via patient registration with a company called Careology, who are specialists homecare medical services. The scheme would apply for administration both within the hospital (Direct Supply to Hospital) and outside of it (Homecare Supply).

Patients who are ≤100kg in weight do not need a scheme of any description. The scheme for >100kg patients is outlined below.

Direct Supply For Hospital Administration

Overview

The Patient Access Scheme for Stelara will be administered through Careology and Polar Speed on behalf of Janssen-Cilag Ltd.

Patient Registration

In order to access the scheme for patients >100kg the prescribing physician (or a HCP nominated by the prescribing physician) will register patients (>100 & <100kg) with Careology Ltd. This registration will be a simple 1-page form which will include the patients' weight and date of initiation of treatment. This form is then faxed directly to Careology Ltd. (This initial registration will easily allow the patient to be converted to home delivery with minimal administration if required).

Patients will be asked to sign a data protection and service consent form to give permission for Careology to hold their data. All data will be held securely on the Careology patient management system.

Patient / Prescription Management

The hospital pharmacy will order Stelara against a specific (pre-registered) patient name. Careology will crosscheck the patients' weight on the registration document and dispatch the prescribed dose and invoice the hospital accordingly, For example, when a 90mg dose is prescribed for a named patient, the patient's weight will be checked and if they are confirmed as being above 100kgs 2 x 45mg vials will be dispatched.

Cold Chain Delivery

Polar Speed Ltd will perform hospital delivery logistics, (specialist temperature controlled pharmaceutical distributor). The cold chain is guaranteed with all Polar Speed sites being MHRA regulated. GPS technology allows real time tracking of vehicle locations and product transit temperatures.

Homecare Supply

Overview

The service to support patients receiving therapy at home will be provided by Careology Ltd and Polar Speed Ltd.

Patient Registration

The prescribing physician will register patients with Careology Ltd, and is the same process in place for other biological products used in psoriasis. This registration will include the patients' weight, in order to ensure correct invoicing through the Patient Access Scheme.

Patients will be asked to sign a data protection and service consent form to give their permission for Careology to hold their data and to allow them to contact patients directly in the normal course of providing the service. All data required to provide the home nursing and delivery will be held securely on the Careology patient management system.
Patients will be provided with a service user guide, which explains how the service works, all relevant contact details for the service, what to do in an emergency and a list of frequently asked questions.

Patients will be given a named service coordinator at Careology who will become the main point of contact for matters relating to deliveries and nursing visits.

Prescription Management

Prescriptions will be faxed to Careology by the dermatologist, hospital pharmacist or dermatology nurse specialist in time for pharmacy dispensing to take place (originals must follow by post). Again, this is the same process as is often used currently with the other biological products used in psoriasis.

The prescription and patient registration document will be crosschecked in order to ensure that billing for patients over 100kg are in line with the scheme.
Careology will notify the prescribing unit when a prescription is due and will work to ensure that patients' therapy is not interrupted.

Deliveries can be "drawn down" from a prescription. That is a prescription may be written for "x" number of dispensing episodes and Careology will dispense, deliver and bill for each episode separately.

Careology will react to changes in prescriptions immediately (e.g. due to changes in dosage prescribed or a patient weight change).

All patients will receive a telephone call from a Careology patient coordinator to confirm delivery requirements prior to a delivery being made.

Pharmacy Dispensing

A UK registered pharmacist will dispense all prescription only medicines. The Careology premises and superintendent pharmacist are registered with the Royal Pharmaceutical Society of Great Britain (RPSGB) and labelling and dispensing complies with the Medicines Act 1968.

Provided Careology have a valid prescription and the patient is registered with the service, delivery can be made next working day as part of the standard service.

Specialist Nursing

All nurses are employees of Careology and receive regular professional training and updates. Careology is subject to the strict regulatory requirements of The Commission for Social Care Inspection and complies with the professional standards of the Nursing and Midwifery Council. All nurses undergo a stringent recruitment process including CRB checks, references, NMC registration status, and competency assessment prior to being allowed to visit patients.

A patient visit form can be sent back to the referring physicians centre after each nurse visit, if requested. Nurses are experienced in administering complex therapies at home and also in training patients to become independent on treatment if appropriate. A nurse visit for each administration episode also ensures compliance on therapy.

Home Delivery

Polar Speed Ltd will perform home delivery. The cold chain is guaranteed with all sites being MHRA regulated. GPS technology allows real time tracking of vehicle locations and product transit temperatures. Careology systems can hold multiple patient delivery points, which allows flexibility between addresses (e.g. main home, work address, GP surgery, UK holiday home). Deliveries are made within an agreed time window. Clinical waste/sharps

bins are removed from patients' home at the time of delivery (appropriate waste carriers licensed are held). Patients sign a proof of delivery as evidence that they have received the delivery.

Specific Circumstances

It is possible for the scheme to operate through other homecare providers and the process would work as follows:

1. The hospital would need to appoint their homecare provider
2. Their provider would need to order direct from Janssen-Cilag Ltd customer services providing a unique patient identifier to permit tracking
3. The homecare provider would be responsible for tracking the PAS, following appropriate training from Janssen-Cilag Ltd.

Figure 1 – Stelara Home Delivery – Patient Access Scheme

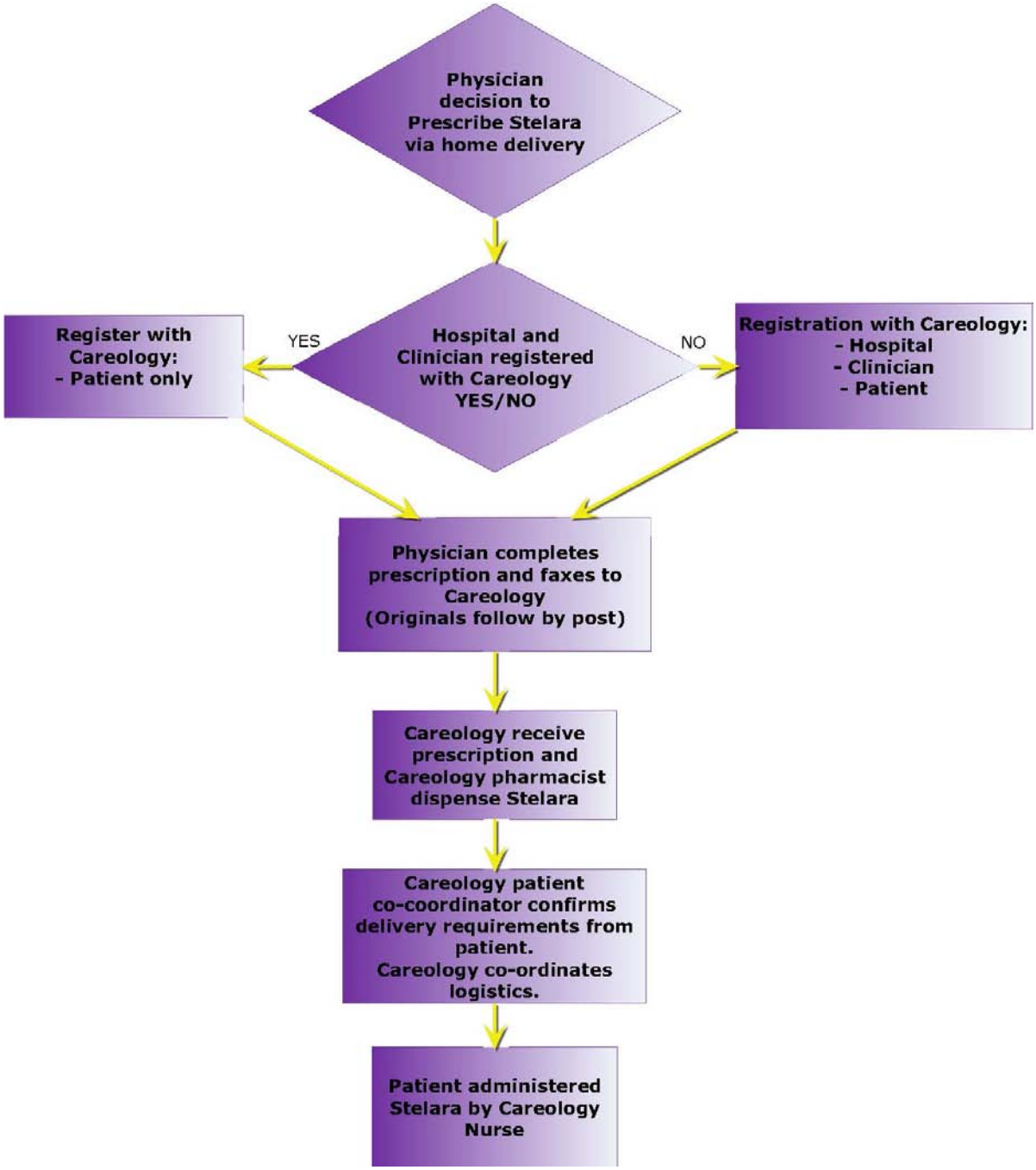

Figure 2 – Stelara Hospital Delivery – Patient Access Scheme