Aberdeen HTA Group

Secukinumab for treating moderate to severe plaque psoriasis

Erratum

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This report was commissioned by
the NIHR HTA Programme as
project number 13/129/01

Contains CIC/AIC

This document is intended to replace pages 22, 59, 60, 62, 64, 65, 98, 101, and 105 of the original ERG assessment report for *Secukinumab for treating moderate to severe plaque psoriasis*, which contained a few inaccuracies.

	Final scope issued by NICE	Decision problem addressed in the submission
		• results from the clinical trial programme) • Health-related quality of life (EQ5D, DLQI)
Economic analysis	• Incremental cost per quality-adjusted life year • Time horizon should be sufficiently long to reflect differences in costs or outcomes between technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • Availability of any patient access schemes for the intervention or comparator technologies should be taken into account • The analyses submitted by the company include the effect of the CIC PAS	• Incremental cost per quality-adjusted life year • 10 year time horizon • Costs considered from an NHS and PSS perspective

5.2.3 Population

The scope specifies patients with moderate to severe plaque psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, or are not tolerated or contraindicated. The patient population is as per the trial entry criteria. For the secukinumab trials the entry criteria corresponded with the scope, with the possible exception of requiring a PASI score of at least 12 coupled with an affected body surface area of at least 10%.

5.2.4 Interventions and comparators

Secukinumab 300mg is compared with:

- Standard of care without biologics (SoC);
- Etanercept 25mg;
- Adalimumab;
- Ustekinumab 45mg;
- Ustekinumab 90mg; and,
- Infliximab 5mg/kg.

5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for benefits and that of the NHS/PSS for costs.

The time horizon is 10 years. Benefits and costs are both discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

The rates of PASI responses are drawn from the network meta-analysis. For the base case the time point for the assessment of response is assumed to be 12 weeks for etanercept, ustekinumab and secukinumab, 10 weeks for infliximab, and 16 weeks for adalimumab. This is described as the NICE time endpoints analysis. An alternative scenario, which assumes that adalimumab is assessed at 12 weeks, is also presented.

Table 14 shows the distribution between PASI response states.

Table 14 Deterministic PASI response rates: base case: NICE time endpoints analysis

	SoC	Secukin.	Adalim.	Etanercept	Ust. 45mg	Ust. 90mg	Infliximab
PASI < 50	88%	7%	23%	39%	13%	10%	8%
PASI 50-74	8%	12%	22%	24%	17%	15%	13%
PASI 75-89	3%	25%	27%	22%	28%	27%	25%
PASI 90-100	1%	55%	28%	15%	42%	48%	54%
PASI 75	4%	80%	55%	37%	70%	75%	80%

Secukinumab is estimated to have a higher point estimate PASI 75 response rate and a higher PASI 90 response rate at 12 weeks than all its comparators with the exception of infliximab. Secukinumab and infliximab have almost identical PASI 75 and PASI 90 response rates. Infliximab has slightly higher PASI <50 and PASI 50-74 response rates than secukinumab.

For the probabilistic analysis a lookup table of 40,000 CODA output iterations is randomly accessed. These 40,000 rows of outputs imply the following mean PASI response rates. The proportion of rows for which each treatment has the highest PASI 75 response rate is also reported.

Table 15 Probabilistic mean PASI response rates: base case: NICE time endpoints analysis

	SoC	Secukin.	Adalim.	Etanercept	Ust. 45mg	Ust. 90mg	Infliximab
PASI < 50	88%	7%	24%	39%	13%	10%	8%
PASI 50-74	8%	12%	22%	24%	17%	15%	13%
PASI 75-89	3%	25%	27%	22%	27%	27%	25%
PASI 90-100	1%	56%	28%	15%	42%	48%	54%
PASI 75	4%	81%	55%	37%	69%	75%	79%
P max PASI75	0%	56%	0%	0%	0%	3%	41%

The probabilistic modelling suggests that secukinumab has the highest probability of having the maximum PASI 75 response rate across the comparators at 56% (Table 15). This is followed by infliximab at 41%, with there being a small 3% probability of ustekinumab having the highest probability of having the maximum PASI 75 response rate across the comparators.

In short, in all of the scenarios considered secukinumab is estimated to be superior to all its comparators in terms of the PASI 75 and PASI 90 response rates. Only for the scenario of the differing NICE assessment time points does infliximab have similar PASI 75 and PASI 90 response rates compared to secukinumab, with the infliximab PASI <50 being slightly more than that of secukinumab and the infliximab PASI 50-74 being slightly more than that of secukinumab.

For the probabilistic modelling it appears that secukinumab has the greatest probability of having the highest PASI 75 response rate across the comparators, with that of infliximab being slightly below this. The probabilities of the other comparators having the greatest probability of having the highest PASI 75 response rate are to all intents and purposes zero.

Serious adverse events: rates

Adverse event rates were taken directly from trial data, SmPCs and Dixon et al 2006,[45,60] rather from any network meta-analysis of these data. It was assumed that SoC was not associated with any of the SAEs.

Table 19 SAE rates

	SoC	Secu.	Etan.	US 45	US 90	Infl.	Adal.
NMSC	0.00000	[redacted]	0.03540	0.00650	0.00650	0.00400	0.00970
non NMSC	0.00000	[redacted]	0.00043	0.00160	0.00160	0.07670	0.00600
Severe infection	0.00000	[redacted]	0.05130	0.01000	0.01000	0.05520	0.05190

Extrapolation

Extrapolation assumes that 20% of those on active treatment discontinue each year, reverting to SoC and a PASI<50 response.

5.2.7 Health related quality of life

Quality of life: by PASI response status

The EQ-5D data across all time points and five trials was pooled in a complete case analysis. A number of functional forms were explored. The ERG assumption is that this was valued using the UK social tariff, though this does not appear to be explicitly stated in the company's submission or the company commissioned utility report. The company chose the

Table 21 Dosing frequency

	Secukin.	Etanercept	Ust 45mg	Ust 90mg	Infliximab	Adalimumab	
Ind. Length	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks	16 wks
Induction	6	24	2	2	3	8	9
Post induction	10	80	4	4	5	20	19
Subs. Annual	12	104	4.33	4.33	6.5	26	26

The dosing for infliximab is 5mg/kg, with it being available in 20mg vials. The number of vials required per dose was based upon an average patient weight of 86.6kg with a standard deviation of 19.8kg (according to the electronic copy of the model, this was derived from Reich et al 2006).[61] While these data may be skewed, an assumption of normality resulted in 9% being under 60kg, 28% being between 60kg and 80kg, 38% being between 80kg and 100kg and 25% being above 100kg. This would imply 3, 4, 5 and 6 vials, respectively with an average estimate of 4.8 vials of infliximab per dose.

Unit costs were drawn from BNF 64 and MIMS, resulting in the direct drug costs presented in Table 22.

Table 22 Direct drug costs

	Secukin.	Etanercept	Ust 45mg	Ust 90mg	Infliximab	Adalimumab	
Ind. Length	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks	16 wks
Unit cost	[redacted]	£89.38	£2,147.00	£2,147.00	£419.62	£352.14	
Induction	[redacted]	£2,145	£4,294	£4,294	£6,030	£2,817	£3,169
Post induction	[redacted]	£7,150	£8,588	£8,588	£10,050	£7,043	£6,691
1st year	[redacted]	£9,296	£12,882	£12,882	£16,081	£9,860	
Subs. Annual	[redacted]	£9,296	£9,297	£9,297	£13,066	£9,156	

[redacted]

[redacted]

Drug administration costs: biologics

The subcutaneous formulations are assumed to require a one off training costs of £39, based upon one hour of nurse time, with this enabling all administrations to be self-administered by the patient. Infliximab administrations are assumed to cost £92.39, based upon the dermatology NHS reference WF01A: non-admitted face to face follow-up, averaged across consultant led and non-consultant led appointments. This results in administration costs for infliximab of £277 during induction and £462 for the remainder of the first year, hence £739 in the first year, and an annual £601 thereafter.

Direct drug costs: SoC

Those on SoC are assumed to receive either methotrexate, ciclosporin or nothing. During years one and two:

- 45% are assumed to require 15mg of oral methotrexate each week;
- 45% are assumed to require 300mg of oral ciclosporin each day;
- 10% are assumed to require no medication.

From year three those on ciclosporin are assumed to cease. Table 23 illustrates the direct drug costs in the SoC arm.

Table 56 Quality of life values of the second company EQ-5D model

	EQ-5D QoL				Δ EQ-5D QoL from baseline			
Model	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
PASI < 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][1]	[redacted]
PASI 90+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A further two models were presented in the second utility report. These models explored the impact of applying a study effect. Adding these to the EQ-5D QoL levels model 3 resulted in FIXTURE, JUNCTURE and SCULPTURE being found to have statistically significant parameters associated with them. Adding the trial interaction effects to the EQ-5D QoL changes from baseline model 7 still resulted in SCULPTURE being found to have a statistically significant parameter, but not FIXTURE or JUNCTURE. The company state that a chi-squared test on the trial coefficients gave a p value of [redacted]

Adding the trial effects to model, the parameter estimates for the other explanatory variables were virtually identical between the model with and without the trial effects. The ERG can confirm that the estimates for the EQ-5D QoL changes from baseline are virtually the same as those of model 7.

Due to the EQ-5D QoL being modelled as a function of the contemporaneous PASI response rather than the PASI response at week 12 the resulting quality of life values are most relevant

[1] This value is given as [redacted] within the company clarification response, with the [redacted] being derived by the ERG from the parameter values. The discrepancy is probably due to rounding errors in the reported parameter values.

These costs are applied in the first, second and third and subsequent years of the model. They are not applied in the first, second and third and subsequent years that patients spend receiving SoC. Within the cohort flows of the biologics most patients typically cease biologic treatment and start SoC after the first or the second year, due to the annual 20% of initial responders assumed to cease treatment. Consequently, patients who start SoC in the second, third and subsequent years avoid the initially higher costs of SoC treatment[m]. This will bias the analysis against SoC.

The correction of the cost calculations within the cohort flow to take this into account would be considerably time consuming. The simpler method employed by the ERG to explore the possible impact of this was to set the first year and second year costs of SoC to be equal to those of the third and subsequent years.

Serious adverse events: resource use

The company's submission costs malignancies as incurring a single inpatient stay, with the costs of these being derived from NHS reference costs. In the opinion of the ERG this seems likely to have missed a number of cost elements which may be quite significant, such as ongoing drug costs. It is also unclear whether all patients would only require a single inpatient stay: some may have none, others may have multiple stays. It is beyond the scope of the ERG report to perform a costing analysis of the identified malignancies (e.g. melanoma, lymphoma and non-melanoma skin cancer). It seems probable that the costs of these have been underestimated.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the company base case to:

- Correct the mortality calculations within the cohort flow[n];
- Revise the QALY calculations for those with a PASI 50-74 response during the first year to apply the PASI <50 quality of life value for the post induction period[o];

[m] This is most easily seen by tracing the dependents of e.g. cell F33 within one of the biologic cohort flow worksheets. There are only dependent cells in the second year; i.e. row 101, and as a consequence any patients discontinuing biologic treatment after the second year do not have these costs applied.

[n] Implemented within the cohort flow calculations by setting cell K101=(K100+(SUM(L100:N100)*H101))*(1-G101), cell L101=(L100-(L100*$H101))*(1-$G101), cell M101=(M100-(M100*$H101))*(1-$G101) and cell N101=(N100-(N100*$H101))*(1-$G101) and cutting and pasting these formulae into cells K102:N114.

[o] Implemented within the *Markov_* worksheets by setting cell L79= IF(Clin_Data_Source=5,16, IF(Clin_Data_Source=1,12,12)) with the exception of adalimumab where L79= IF(Clin_Data_Source=5,16, IF(Clin_Data_Source=1,12,16)) and infliximab where L79= IF(Clin_Data_Source=1,12,10)), and M79=52-L79

for secukinumab compared to SoC is around £30,000 per QALY. If the mean annual numbers of day case admissions and days as an inpatient together total around 14 the cost effectiveness estimate for secukinumab compared to SoC is around £20,000 per QALY.

Sensitivity analyses explore the impact of:

- Etanercept requiring only 1.33 administrations rather than 2.00 administrations after induction[z], as inferred by the ERG from TA103.[43] Note that this is perhaps an extreme value, and it might be more reasonable to use the 1.82 of Lloyd et al 2009;[57]
- Reducing the secukinumab discontinuation rate subsequent to the first year to 15%[aa];
- Varying the discontinuation rate subsequent to the first year to 15% and 25%[bb];
- Setting the first year discontinuation rate to zero[cc];
- An arbitrary increase in mortality risk of 20% associated with psoriasis[dd];
- Flattening the SoC costs so that costs in years one and two of the model are the same as in subsequent years[ee];
- Arbitrarily doubling the SAE costs of the biologics[ff];
- Revising the quality of life impacts to be from the various NICE assessments or EQ-5D models submitted by the company[gg]

[z] Implemented within the *Tx_cost_calculations* by conditioning cells F180 and E189 by 1.33/2.
[aa] Implemented within the *Markov_trace_SEC_300* worksheet by setting cell F19=0.15.
[bb] Implemented within the *Drop_out_calculations* worksheet by setting cell H30 equal to the appropriate value.
[cc] Implemented within the *Drop_out_calculations* worksheet by setting cell H23=0.
[dd] Implemented within the *Mortality_Inputs* worksheet by multiplying the values within cells N9:N89 by 1.2.
[ee] Implemented within the Monitoring_costs_calculations worksheet by setting cells Q22=12/52*P50 and P37=(52-12)/52*P50, and within the Tx_cost_calculation worksheet by setting cells E238=12/52*H238, F238=(52-12)/52*h238 and G238=H238.
[ff] Implemented within the *Adverse_event_calculations* worksheet by doubling the values in cells G30:G32.
[gg] Implemented within the *Utility_calculations* worksheet by setting cells G11:G15 to the relevant values.