

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Secukinumab for treating moderate to
severe plaque psoriasis**

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

- 1.1 Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when:
- the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
 - the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them
 - the company provides secukinumab with the discount agreed in the patient access scheme.
- 1.2 Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these people. An adequate response is defined as either:

- a 75% reduction in the PASI score from when treatment started (PASI 75) or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

1.3 People whose treatment with secukinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

1.4 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

2 The technology

2.1 Secukinumab (Cosentyx, Novartis) is a high-affinity, fully human monoclonal antibody that binds to and neutralises interleukin-17A, which is thought to be involved in the body's autoimmune response in diseases such as psoriasis. Secukinumab has a marketing authorisation for 'the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy'.

2.2 The summary of product characteristics includes the following adverse reactions for secukinumab: upper respiratory tract infections (most frequently nasopharyngitis, rhinitis), oral herpes simplex, rhinorrhoea, diarrhoea and urticaria. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Secukinumab is given subcutaneously. The recommended dosage is 300 mg at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. The undiscounted price for 2 x 150 mg

prefilled pen or syringe is £1218.78 (excluding VAT, 'Monthly Index of Medical Specialities' [MIMS] May 2015). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

Overview of the clinical trials

- 3.1 The company did a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of secukinumab for treating people with moderate to severe chronic plaque psoriasis. It identified 5 relevant international, multicentre, phase 3, double-blind, randomised, controlled trials: 3 superiority trials compared secukinumab with placebo (ERASURE; JUNCTURE; FEATURE) and 1 compared secukinumab with both placebo and etanercept (FIXTURE). Another trial (SCULPTURE) was a non-inferiority trial comparing 2 different dosing regimens of secukinumab: a regular dose regimen of secukinumab compared with re-treatment with secukinumab only at relapse.
- 3.2 The company did not find any other head-to-head studies, and therefore did a network meta-analysis to compare secukinumab with all 5 comparators identified in the scope (best supportive care,

etanercept, ustekinumab, adalimumab and infliximab). The company did not find any relevant non-randomised controlled or observational studies.

3.3 The 4 placebo-controlled trials (FIXTURE, ERASURE, JUNCTURE and FEATURE) had similar designs. Patients were stratified by either body weight alone (90 kg or more or less than 90 kg), or geographical location and body weight, and randomised to secukinumab 300 mg or 150 mg, or placebo. Secukinumab was given at weeks 0, 1, 2, 3, and 4, and then 4-weekly. The FIXTURE trial also included an etanercept comparator arm (50 mg twice a week initially, then 50 mg once per week). At week 12, patients in the placebo arms who did not have a Psoriasis Area Severity Index (PASI) of 75 (that is, had not had a 75% reduction in the absolute PASI score from baseline; the primary outcome) were 're-randomised' to either 150 mg or 300 mg secukinumab (at weeks 12, 13, 14 and 15 from baseline, followed by the same dose every month from week 16). All trials had a placebo-controlled period lasting 12 weeks followed by a 40-week maintenance period. However, patients completing JUNCTURE and FEATURE were followed for a further 156 weeks.

3.4 Patients were eligible for inclusion in the trials if they had moderate to severe chronic plaque psoriasis not adequately controlled by topical treatment, phototherapy or previous systemic therapy. Severity was defined as: the percentage body surface area affected by psoriasis, absolute PASI score, and the Investigator Global Assessment score (modified in 2011, hereafter referred to as IGA). IGA is a 5-point scale that measures psoriasis severity ranging from 0 (clear) to 4 (severe disease). To be eligible, patients needed to have 10% or more of their body surface area affected by psoriasis, a PASI score of 12 or more, or an IGA score of 3 or more. Patient characteristics were generally similar across the

trials, with some differences. For example, FIXTURE and ERASURE had a lower proportion of patients who had received prior biological treatments (Range: 10.7% to 29.4% across trials and trial arms) than JUNCTURE and FEATURE (21.3% to 47.5% across trials and trial arms); and FEATURE and ERASURE had a higher proportion of patients for whom a prior biological had failed. Across trials, previous systemic therapies (including methotrexate) ranged from 33.9% (FEATURE, secukinumab 300 mg arm) to 62.6% (FIXTURE, etanercept arm).

- 3.5 The company presented clinical trial results for secukinumab both at 150 mg and 300 mg. The marketing authorisation, however, is only for 300 mg. Therefore, this final appraisal determination presents only the results for the licenced dose (300 mg) (hereafter referred to as secukinumab).
- 3.6 The co-primary outcome measures in all 4 placebo-controlled trials were measured at week 12: PASI 75 (that is, a 75% reduction from baseline in PASI score), and an IGA score of 0 or 1 (indicating clear or almost clear of disease). The PASI response was used in the model and the network meta-analysis. Therefore, this final appraisal determination presents results only for PASI outcomes. The company analysed the data using intention-to-treat methods. The company reported odds ratios for FIXTURE and ERASURE, and 'risk differences' (the difference in proportions of patients in whom the outcome was reached) for JUNCTURE and FEATURE. In all 4 placebo-controlled trials, there were statistically significant improvements with secukinumab in the co-primary outcomes compared with placebo. For example, across trials, at week 12, 75.9% to 86.7% of patients randomised to secukinumab had a PASI 75 response, compared with a 0% to 4.9% ($p < 0.0001$ all trials) of patients randomised to placebo. There were also statistically significant improvements with secukinumab compared

with etanercept. PASI 75 response was 77.1% with secukinumab compared with 44% with etanercept ($p < 0.0001$). The company also noted that response to secukinumab for these outcomes continued to increase between week 12 and week 16 in the FIXTURE and ERASURE trials.

- 3.7 Secondary outcomes in the placebo-controlled trials included assessing PASI 75 at different time points (weeks 16 and 52), different PASI responses, for example, at week 12, PASI 50/90/100 responses, and maintenance of PASI 75 and health-related quality of life. The effectiveness of secukinumab for these secondary outcomes were consistent with the results for 12-week PASI 75 in that there were improvements with secukinumab compared with placebo across the 4 placebo-controlled trials (statistical significance was achieved for some outcomes, but the company did not perform or present statistical analyses for all outcomes). For example, week-12 PASI 100 (that is, complete clearance of the disease) ranged from 24% to 43% for secukinumab (across all trials), was 4.3% for etanercept (FIXTURE trial) and ranged from 0% to 0.8% for placebo. In the FIXTURE trial at week 52, 36.2% of patients had a PASI 100, which was higher than with etanercept (9.9%). The company had not predefined this as an outcome, so did not do statistical analyses.
- 3.8 The company provided the results of analyses of primary and secondary trial outcomes for pre-specified subgroups that included sex, age, weight, geographic location, age at diagnosis, disease duration, quality of life and previous experience of other treatments (biological and non-biological). The company provided these as 'academic in confidence' but noted these were consistent with the main results.

- 3.9 The company presented results on the effect of secukinumab on the dermatology life quality index (DLQI) score in all 4 placebo-controlled trials. In all the trials, secukinumab improved (that is, reduced) DLQI score at week 12 from baseline by between 10.4 to 11.6 points, which was higher than with placebo (1.1 to 1.9 points; $p < 0.001$ for all trials other than FIXTURE, in which no p value was given). The company stated that these improvements were maintained at week 52 in the FIXTURE and ERASURE trials. The number of people with a week 12 DLQI response of 0 or 1 (that is, showing no impact on daily living) was statistically significantly higher for secukinumab in all trials than with placebo ($p < 0.001$) and etanercept ($p < 0.001$).
- 3.10 The company presented evidence on the absolute changes from baseline in quality of life with secukinumab compared with placebo based on a EQ-5D visual analogue scale of 0 (worst possible health state) to 100 (best possible health state), which were statistically significantly higher with secukinumab than with comparators in all 4 placebo-controlled trials.

Meta-analyses/indirect comparison/MTC

- 3.11 The company compared secukinumab with the other biological comparators (adalimumab, etanercept, infliximab and ustekinumab) using a random effects network meta-analyses. The network meta-analysis presented for each treatment the effectiveness reflected by PASI response from baseline (less than 50%, 50–74%, 75–90%, 90% or more). The company identified 30 relevant trials for the network meta-analyses from its systematic literature review, including the 5 relevant secukinumab trials (as described in sections 3.1 to 3.10) and 25 trials for the comparator treatments. However, the company did not include all trials in all its analyses. Doses included in the base-care analysis are described in table 1.

The company excluded some studies or arms that had tested

irrelevant doses or comparators. However, it included a 150 mg dose arm for secukinumab and a 100 mg arm for etanercept (16-week scenario only) to connect the network.

Table 1 Interventions and doses of interest used in base case

Drug	Induction phase	Maintenance dose
Secukinumab	150 mg or 300 mg weeks 0,1,2,3 and 4	150 mg or 300 mg every month
Etanercept	25 mg twice weekly for 12 weeks	25 mg twice weekly or 50 mg weekly
Infliximab	5 mg/kg weeks 1,2 and 6	5 mg/kg every 8 weeks
Adalimumab	80 mg week 1	40 mg every 2 weeks
Ustekinumab	45 mg or 90 mg weeks 1 and 4	45 mg or 90 mg every 12 weeks

3.12 The base-case network meta-analyses presented the PASI response after ‘induction’ assessed at 10 weeks (infliximab), 12 weeks (secukinumab, etanercept and ustekinumab) or 16 weeks (adalimumab) (see table 2). The company also presented 2 scenario analyses: a 12-week analysis (assessing effectiveness at 12 weeks for each treatment) and a 16-week analysis (repeating the base case, but using 16-week assessment for secukinumab only). In the base case, the network meta-analysis showed that secukinumab 300 mg was statistically significantly more effective than placebo, secukinumab 150 mg, etanercept and adalimumab in achieving a 50%, 75% and 90% reduction in PASI. There were no statistically significant differences when comparing secukinumab 300 mg with ustekinumab or infliximab. Results for the scenario analyses were consistent with the base case. The company stated that similar results were seen with sensitivity analyses including the following populations: DLQI of more than 10 (other than adalimumab, for which comparisons were not possible); duration of

psoriasis; baseline PASI score; and prior exposure to biological drugs. The company also reported that it showed similar results with a meta-regression adjusting for prior biological exposure.

Table 2 Base-case network meta-analyses. Treatment effect (relative risk) and credible intervals; secukinumab 300 mg compared with all treatments

Comparator	PASI 75	PASI 50	PASI 90
Placebo	22.25 (18.7 to 26.62)	7.99 (7.05 to 9.11)	92.53 (71.67 to 119.3)
Secukinumab 150 mg	1.17 (1.10 to 1.26)	1.08 (1.05 to 1.12)	1.36 (1.22 to 1.54)
Etanercept	2.15 (1.76 to 2.71)	1.52 (1.35 to 1.75)	3.71 (2.69 to 5.33)
Ustekinumab 45 mg	1.15 (1.05 to 1.28)	1.07 (1.02 to 1.12)	1.3 (1.09 to 1.61)
Ustekinumab 90 mg	1.07 (0.98 to 1.19)	1.03 (0.99 to 1.08)	1.15 (0.96 to 1.4)
Adalimumab	1.46 (1.26 to 1.76)	1.21 (1.12 to 1.34)	2.0 (1.54 to 2.76)
Infliximab	1.01 (0.92 to 1.13)	1.0 (0.96 to 1.05)	1.02 (0.84 to 1.28)
Abbreviation: PASI, Psoriasis Area Severity Index			

3.13 All trials captured adverse effects of treatment. The most commonly reported adverse effects for secukinumab were nasopharyngitis, headache, diarrhoea, upper respiratory tract infection, itching and fever. In FIXTURE, ERASURE, FEATURE and JUNCTURE, the proportion of patients who developed any adverse event with 300 mg secukinumab (50.8% to 70.0%) was higher than with placebo (47.0% to 54.1%). The FIXTURE study showed similar rates of any adverse events at week 52 for secukinumab and etanercept (252.0 and 243.4 cases per 100 patient years respectively). The secukinumab 300 mg arm showed no increase in safety-related events than the 150 mg arm.

ERG comments on the clinical effectiveness

- 3.14 The ERG stated that the systematic review done by the company was of good quality, and appeared to be complete because it included the 4 main clinical trials (FIXTURE, ERASURE, JUNCTURE, and FEATURE). The ERG considered the clinical trials to be of good quality, and the review of clinical evidence was generally well-conducted, with an appropriate assessment of bias. The ERG stated that patients in the clinical trials were appropriately randomised and allocated to treatment, and baseline demographics and disease characteristics were balanced across intervention groups. The ERG stated that there was strong evidence that secukinumab 300 mg is superior to placebo for PASI efficacy outcomes at week 12.
- 3.15 The ERG stated that the description of the network meta-analysis, the method used to conduct the network meta-analysis, and the method used to evaluate consistency between direct and indirect evidence, were all generally appropriate. However, the ERG noted several issues, including that the company had meta-analysed 1 outcome only, and it would also have been possible to present meta-analyses for quality of life.
- 3.16 The ERG reviewed the adverse event information presented in the company submission. The clinical adviser to the ERG had noted that, because biological treatments suppress the immune system, this may increase rates of cancer. The clinical adviser also stated that there is no evidence for an increase in lymphoma with biological treatment for people with psoriasis, that phototherapy can increase the risk of both melanoma and non-melanoma skin cancer, and that prolonged ciclosporin treatment has been associated with lymphoma.

Cost effectiveness

- 3.17 The company did not identify any relevant cost-effectiveness analyses for secukinumab in its systematic review. For the comparator etanercept, it identified 2 studies (Woolacott et al., 2006, Lloyd et al., 2008).

Model structure

- 3.18 The company developed a new economic model that combined a decision tree with a Markov state-transition model to compare secukinumab 300 mg with etanercept, ustekinumab (45 mg and 90 mg), adalimumab, infliximab and best supportive care. The model applied to adults with moderate to severe plaque psoriasis (defined as absolute values of PASI 10 or more and DLQI more than 10) whose disease had inadequately responded to at least 2 standard systemic therapies. The model had a 10-year time horizon (1-year decision tree followed by 9-year Markov model) with 3 key time periods: an induction phase (12–16 weeks depending on the pharmaceutical agent); a post-induction to 1-year phase; and an annual phase (9 years). Within each phase, patients could be in 1 of 4 health states based on the response from baseline in PASI (PASI less than 50%, 51–74%, 75–90%, more than 90%), plus a state reflecting death. The company assigned resource use, costs and quality-adjusted life years (QALYs) for each of these health states. The company conducted the analysis from the perspective of the NHS and Personal Social Services, and discounted costs and health effects at an annual rate of 3.5%.
- 3.19 Patients entered the decision tree at the beginning of the induction period, the duration being determined by which drug they were taking, (that is, 12 weeks for secukinumab, ustekinumab and etanercept, and 10 and 16 weeks respectively for infliximab and adalimumab). Patients remained on treatment for the whole

induction period. If, after the induction period, a patient's disease had not responded (that is, their PASI had not improved by 75% or more) the biological treatment was stopped and the patient moved on to best supportive care and into the PASI less than 50 health state. In the best supportive care state, treatments included systemic therapies (90% received either methotrexate or ciclosporin) and phototherapy (16%), and all patients were assumed to receive day centre care (psoriasis day-case admission), based on the costing template for NICE's guideline on [psoriasis](#). Patients whose disease responded to treatment during the induction phase (that is, patients who had a PASI 75 or above) continued on treatment for 1 year. At 1 year, the company assumed a discontinuation rate based on the FIXTURE and ERASURE trials of 11.7% for patients who stopped treatments with biological drugs and moved to the PASI less than 50 state and who received treatment with best supportive care. All other patients progressed into the annual Markov model, with a 20% annual all-cause discontinuation rate (based on expert opinion) applied beyond 1 year. The company assumed that, after the induction period, patients did not change PASI health states; patients either remained in their PASI health state and accrued the costs and benefits of that health state, or transitioned to best supportive care (PASI less than 50 health state) or death. The company noted that, although people with severe psoriasis have a reduced life expectancy because of cardiovascular disease, lymphoma and non-melanoma skin cancer, it did not model disease-specific mortality rates. Instead, the company used age-specific all-cause mortality rates from the general population.

Company model details

Effectiveness

- 3.20 The company populated the model with the pooled clinical efficacy estimates for PASI 75 taken from its base-case network meta-analysis (see sections 3.11 to 3.13), which estimated the probabilities of people reaching the various PASI health states by treatment. The company chose a population cohort aged 45 years based on FIXTURE and ERASURE data.
- 3.21 The response reflected by PASI following induction for each comparator is shown in table 3 and are maintained for the remainder of the model.

Table 3 Percentage of patients having a given PASI response state at the end of the induction period

Treatment	PASI improving by <50%	PASI improving by 50–74%	PASI improving by 75–89%	PASI improving by 90% or more
Best supportive care	88.4%	8.0%	3.0%	0.6%
Secukinumab 300 mg	7.3%	12.5%	24.8%	55.4%
Adalimumab	23.4%	21.7%	27.2%	27.7%
Infliximab	7.7%	12.8%	25.1%	54.4%
Ustekinumab 45 mg	13.0%	17.0%	27.5%	42.4%
Ustekinumab 90 mg	10.1%	15.0%	26.6%	48.3%
Etanercept	39.1%	23.7%	22.3%	14.9%

Abbreviation: PASI, Psoriasis Area Severity Index

Utility values

- 3.22 To model health-related quality of life, the company converted EQ-5D data from the 5 secukinumab trials into utility increments for each PASI health state using a regression analysis that took into account both PASI and DLQI scores to predict the utility values. In sensitivity analyses, the company considered utility values from a previous NICE technology appraisal on [adalimumab for the](#)

[treatment of adults with psoriasis](#) and from a systematic review of the literature for people with psoriasis. The company considered the EQ-5D utility data the most robust data because it was collected directly in the secukinumab trials. The company noted that the EQ-5D utility values used in the model were between the estimates identified in the literature and in prior NICE technology appraisals. The company stated that although adverse events were not captured explicitly in the model because not enough information was available, adverse events were indirectly captured through the use of EQ-5D in the trials, and response rates and all-cause discontinuation in the model. Table 4 shows the company's base-case utility values and alternative utility values from previous NICE technology appraisals.

Table 4 Utility values: Base case (pooled secukinumab trials) and alternative values

	PASI less than 50	50–74	75–89	90 or more
Utility value used in base case				
Pooled baseline	0.642			
Secukinumab trials pooled change from baseline	0.11	0.19	0.23	0.26
Utility values used in previous NICE technology appraisals (change from baseline)				
Etanercept TA103	0.05	0.17	0.19	0.21
Adalimumab TA146	0.054	0.14	0.14	0.219
Adalimumab TA146 DLQI 10 or less	0.045	0.102	0.102	0.13
Adalimumab TA146 DLQI more than 10	0.063	0.178	0.178	0.308
Infliximab TA134	0.12	0.29	0.38	0.41
Ustekinumab TA180	0.04	0.17	0.22	0.25
Note: base-case utility values were taken from pooled secukinumab trial data. Adalimumab utility values used in a scenario analysis				
Abbreviations: DLQI, dermatology life quality index; TA, technology appraisal				

Modelled resources

- 3.23 The company described the resource use for the treatment of moderate to severe psoriasis, which included drug costs, administration costs and monitoring costs. The company used sources including the British National Formulary (edition 64) and NHS reference costs to populate costs in the model. The company based the resource use associated with best supportive care on the costing template for NICE's guideline on [psoriasis](#). The company used expert opinion to validate its assumptions on frequency of physician and monitoring visits.
- 3.24 The company did a systematic review to identify relevant costing studies. One relevant study identified was by Fonia et al. (2010). This reported the results of a retrospective observational study that compared resource use, costs and disease severity for people with moderate to severe psoriasis in the 12 months before and the 12 months after treatment with biologicals. The analysis showed that the mean annual hospital costs decreased by £1682 in the 12 months after starting biological treatment, and mean annual drug costs increased by £9456. The company stated that it excluded this study in its analyses of cost effectiveness when costing best supportive care because NICE's [psoriasis](#) guideline and expert opinion were more up to date.
- 3.25 The dosing frequency with biologicals was based on the summary of product characteristics. People receiving subcutaneous biological treatments (secukinumab, adalimumab, ustekinumab and etanercept) were assumed to administer their own treatment (after a one-off training cost of £39.00). The company assumed that the administration costs for infliximab (administered intravenously) included an appointment with the dermatologist for administration (£92.39).

- 3.26 For all treatments, the costs of patient monitoring included the costs of visiting a physician (£98.00) and the cost of various monitoring tests (total cost £6.76) based on NHS reference costs. The frequency of the visits varied from 3 to 5 visits during the induction and post-induction periods and thereafter 4 visits annually for most treatments (and 6 annually for infliximab). People on best supportive care also accrued costs for phototherapy (£91 at a frequency of 3.84 visits annually) and day centre care (£460 at a frequency of 5 visits annually), with 1 to 4 visits in the induction and post-induction periods for both treatments.
- 3.27 The company included the costs of hospitalisation for exacerbations of psoriasis, non-melanoma skin cancer, other malignancies and severe infection. For a flare of psoriasis, the company applied a cost once annually of £5337.20 to people who either started treatment with best supportive care, or switched to best supportive care because their disease had not responded to or had stopped responding to biological treatment. The company calculated the cost of hospitalisation using a weighted average of several psoriasis-related Healthcare Resource Group (HRG) codes to reflect an average rate per day (£498.80), which it then multiplied by average length of stay (10.7 days based on hospital episode statistics [HES]). Rates for both non-melanoma skin cancer (£1460.49) and other malignancies (lymphoma [£8178.26] and malignant melanoma [£1460.49]) were taken either from trial data for secukinumab or from the summary of product characteristics for the other biologicals. The company estimated the rates and associated costs of severe infection (sepsis, tuberculosis, pneumonia, skin, soft tissue, bone, joint, and urinary tract) from trial data for secukinumab, the summary of product characteristics for ustekinumab, or a study by Dixon et al. (2006) that reported serious infection rates associated with etanercept, infliximab and

adalimumab in people with rheumatoid arthritis. The company estimated the proportion of people receiving phototherapy from NICE's [psoriasis](#) guideline.

Company's base-case results and sensitivity analysis

3.28 The company's base-case results for the cost effectiveness of secukinumab (based on a model updated with a correction to utility values, which had a minor impact on cost-effectiveness results) were presented as an incremental analysis of secukinumab and other biological treatments. The incremental cost-effectiveness ratio (ICER) for secukinumab compared with etanercept was £2515 per QALY gained (incremental costs £573, incremental QALYs 0.22) in the incremental analysis and secukinumab dominated all other biological treatments (adalimumab, ustekinumab 45 mg and 90 mg, and infliximab). The ICER for secukinumab compared with best supportive care was £7231 per QALY gained (incremental costs £2752, incremental QALYs 0.38).

Company scenarios

One-way sensitivity analyses

3.29 The company did one-way sensitivity analyses varying a range of parameters including the price of secukinumab, discounting (costs and health effects; 0% and 5%), the effectiveness of secukinumab, discontinuation rates for biological therapies, adverse event rates, costs (drug, monitoring and hospitalisation costs varied by +/- 20%) and resource use (administration of treatments and monitoring varied by +/- 20%). The one-way sensitivity analyses showed in most scenarios that, compared with either best supportive care or with the other biologicals, secukinumab dominated. The company noted that the most common key drivers across all of the comparisons were the costs of treatment, the frequency of dosing, the cost and length of stay associated with

hospitalisation, and the relative treatment effects. When the cost of the comparator drug was reduced by 20%, the ICER for secukinumab increased to over £20,000 per QALY gained.

Scenario analyses

3.30 The company did 5 scenario analyses to examine the structural assumptions and data sources used in its base case. One scenario included the possibility that people whose disease partially responds to treatment (PASI 50–74) continued treatment. Two scenarios used different outcomes from the network meta analyses (outcomes at 12-week or 16-week analyses; see sections 3.11 to 3.13). Another scenario used utility values from NICE's technology appraisal on [adalimumab for the treatment of adults with psoriasis](#), while another used 12-week data reflecting PASI response from FIXTURE for secukinumab, etanercept and placebo. Compared with best supportive care, the ICER for secukinumab varied from £4834 ('partial responder' scenario) to £9166 (FIXTURE data scenario) per QALY gained. Compared with etanercept, the ICER for secukinumab varied from £2345 (utility values scenario) to £3732 (16-week scenario) per QALY gained. Secukinumab continued to dominate adalimumab, ustekinumab (45 mg and 90 mg) and infliximab in all scenarios.

Probabilistic sensitivity analyses

3.31 The company did probabilistic sensitivity analyses with 5000 simulations employing parameters including efficacy, adverse event rates, discontinuation rates, utility values, resource use and costs of monitoring. Secukinumab dominated infliximab, ustekinumab 45 mg, ustekinumab 90 mg and adalimumab in most scenarios. Secukinumab was more effective and more costly than etanercept. A cost-effectiveness acceptability curve showed that secukinumab had the highest probability (close to 100%) of being the most cost-

effective treatment at a maximum acceptable ICER of £20,000 per QALY gained compared with best supportive care, etanercept, adalimumab and ustekinumab 45 mg. The cost-effectiveness acceptability curve also showed that secukinumab had a higher probability of being cost effective than infliximab (58%) and ustekinumab 90 mg (93%) at a maximum acceptable ICER of £20,000 per QALY gained.

ERG comments on cost effectiveness

- 3.32 The ERG stated that the company appeared to have found the relevant evidence for economic evaluations and data on health-related quality of life. The ERG's expert stated that, although people can take etanercept intermittently, in clinical practice, any effective biological is likely to be used continuously, as modelled by the company in its base case. The ERG calculated that intermittent dosing of etanercept would be given at a frequency of 1.33 doses per week, compared with 2 doses per week used assuming continuous dosing.
- 3.33 The ERG noted that the health economic model was similar to models used in previous NICE appraisals for psoriasis. Notably, previous models had assumed that people with severe psoriasis that fails to respond to a biological are then given best supportive care. However, the ERG's clinical adviser stated that this was not realistic because, in clinical practice, people would switch to another biological treatment, or add treatments (for example, methotrexate or phototherapy). The ERG stated that a more appropriate model would take into account treatment sequencing.
- 3.34 The ERG queried why the company had applied a discontinuation rate at the end of year 1 because the model already assumed that people whose disease had not responded to treatment stopped treatment. The ERG's clinical expert noted that a rate of 15% to

20% per year was a reasonable estimate for the proportion of patients who stop treatment annually beyond the first year.

- 3.35 The ERG noted that the company did not model an increased risk of mortality for people with psoriasis and did not account for deaths during the first year or after people had stopped treatment. The ERG considered that this may have biased the model against the more effective treatments.
- 3.36 The ERG noted the company's assumptions that people remain in a given health state from the end of the induction period for the duration of the model. However, the ERG also noted that data from the FIXTURE trial showed that over time most people with either a PASI 50–74 or PASI 75–90 at week 12 either improved or worsened over time. The ERG noted that most people with a PASI 90 response at week 12 maintained their response to 52 weeks.
- 3.37 The ERG considered the company's approach to modelling quality of life, noting that modelled utility values depend on a patient's health state. However, in reality, a treatment in itself may influence a patient's health-related quality of life. The ERG considered that this would bias the cost-effectiveness estimates against secukinumab. The ERG considered that the EQ-5D was unlikely to capture the disutility associated with adverse events because the company had stratified the EQ-5D data by PASI response, rather than by treatment arm. The ERG also noted that the company had calculated QALYs accrued in the first year assuming that the amount a patient's disease had responded by week 12 was maintained for up to 1 year. The ERG stated it would be more appropriate for people whose disease responds partially with a PASI 50–74 to accrue the quality of life for PASI 50–74 for the induction period (weeks 0–12), and then the quality of life

associated with PASI more than 50 for the remaining period of the first year because people whose disease partially responds stop treatment from week 12.

3.38 The ERG noted a number of issues with the calculation of the costs of best supportive care. The ERG noted that the Fonia et al. (2010) study (see section 3.24) showed that biologicals had a lower impact on the use of healthcare resources (in particular, hospital admissions) than the estimates used by the company derived from the costing template for NICE's [psoriasis](#) guideline.

3.39 The ERG considered it optimistic that all people receiving biological treatments could self-administer subcutaneously after only 1 hour of training. It considered the estimate from NICE's technology appraisal guidance on [etanercept and efalizumab for the treatment of adults with psoriasis](#), which assumed 3 × 1-hourly sessions of training for self-administration to be a more reasonable estimate, and used this in the ERG's base case.

3.40 The ERG conducted an exploratory analysis of the company's base case (based on the company's original base case, before the minor corrections for utility values, see section 3.28). The ERG:

- removed the costs of 5 intravenous infusions that the company had incorrectly attributed to secukinumab
- included the costs of serious adverse events for patients taking biologicals for the first year, which the company had omitted from the model
- updated the number of doses of secukinumab and ustekinumab because the ERG interpreted the licensing information for dosing differently to the company:

- for secukinumab, the ERG interpreted the dosing as 4-weekly, which would be 13 doses annually, and not 12 as modelled by the company
- for ustekinumab, it stated that the post-induction dose would be 3 doses, and not 4 as modelled by the company
- corrected mortality calculations within the cohort because the company had originally assumed that patients who stop treatment do not die
- revised the QALY calculations for people whose disease partially responds and therefore stop treatment, by applying the PASI less than 50 quality-of-life value for the post-induction period
- removed the hospitalisation cost for people with a PASI 75 response remaining on drug therapy in the best supportive care arm
- removed the costs of hospitalisation in the first year among people with a PASI 50–74 response from week 0 to week 12 and instead calculated the costs from week 12 to week 52 (to remove hospitalisation costs included in the induction period)
- revised the utility values to reflect those supplied by the company to the ERG during the clarification phase of the appraisal
- revised the time a nurse needs to teach a patient to inject subcutaneous biologicals from 1 hour to 3 hours
- revised the mean patient weight to 83.3 kg, which the ERG took from the FIXTURE trial.

3.41 The ERG presented 2 different base cases reflecting 2 alternative sources of costs for the best supportive care. Both base cases incorporated the ERG's corrections to the model:

- Base case A: This scenario (the ERG's preferred scenario) used assumptions related to best supportive care based on Fonia et

al. (2010; an average increase of 5 inpatient days, an average increase of 3 phototherapy sessions and no increase in the average number of day centre care attendances when compared with biological treatments).

- Base case B: This scenario used assumptions related to best supportive care based on the costing template for NICE's [psoriasis](#) guideline and hospital episode statistics data (an average increase of 10.7 inpatient days, an average increase of 3.84 phototherapy sessions and an average increase of 5 day centre care attendances when compared with biological treatments).

3.42 The ERG's preferred exploratory base case generated an ICER of £52,760 per QALY gained (incremental costs £20,087, incremental QALYs 0.38) for secukinumab compared with best supportive care. Secukinumab extendedly dominated etanercept, adalimumab and ustekinumab, and secukinumab dominated infliximab (an option is 'extendedly dominated' when its ICER is higher than that of the next, more effective, option when compared with a common baseline). The ICERs for secukinumab, when compared directly with etanercept, adalimumab, ustekinumab 45 mg and ustekinumab 90 mg, were £42,367, £38,684, £26,321 and £17,717 per QALY gained respectively. The ERG's exploratory base case B used the company's preferred source of data for best supportive care and generated an ICER of £14,902 per QALY gained (incremental costs £5673, incremental QALYs 0.38) for secukinumab compared with best supportive care. Secukinumab extendedly dominated etanercept and adalimumab, dominated ustekinumab and infliximab, and had an ICER compared with etanercept and adalimumab of £8899 and £6979 per QALY gained respectively.

3.43 The ERG presented sensitivity analyses to explore the impact of:

- intermittent dosing of etanercept (see section 3.32)
- alternative discontinuation rates
- increasing the mortality risk associated with psoriasis of 20%
- making the costs of best supportive care consistent throughout the model by reducing the costs of year 1 and 2
- alternative quality-of-life estimates from previous technology appraisals and EQ-5D models submitted by the company.

3.44 The ERG presented results of its sensitivity analyses for base cases A and B. The ERG noted that changing the dosing of etanercept to intermittent dosing worsened the cost effectiveness of secukinumab compared with etanercept from £42,368 per QALY gained to £59,268 per QALY gained (base case A), and from £8899 per QALY gained to £25,800 per QALY gained (base case B). Using utility values from NICE's technology appraisal on [infliximab for the treatment of adults with psoriasis](#) decreased the ICERs for secukinumab to less than £27,000 per QALY gained when using utility values (using base case A). The ERG noted that varying the price and effectiveness of the biologicals influenced cost effectiveness more than other variables.

3.45 Full details of all the evidence are in the [Committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of secukinumab, having considered evidence on the nature of psoriasis and the value placed on the benefits of secukinumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the patient and clinical experts about the experience of people with psoriasis. It heard that the disease

results in itchy, dry, scaly and thickened skin, which can be physically and psychologically debilitating, particularly if located on the hands, feet and genitals. The Committee heard that, because psoriasis is visible, it can make people feel isolated and lonely, which could lead to them losing self-confidence and avoiding social situations, and could also affect career opportunities and influence intimate relationships. The Committee agreed that severe psoriasis substantially decreases quality of life.

- 4.2 The Committee considered the treatment pathway for people with psoriasis. The Committee heard that complete clearance of disease is the goal of treatment. It heard from the clinical experts that, in practice, as first-line treatment people receive topical treatments, systemic non-biological therapies (such as methotrexate), and phototherapy. The Committee was aware that these treatments may be associated with adverse effects and patients need monitoring for such effects; generate hospitalisation costs; have a limited lifetime exposure (for example, phototherapy because of the risk of developing skin cancer); and can be inconvenient for patients (for example, because of frequent hospital visits for monitoring or treatment administration). The Committee heard that clinicians may limit the use of tumour necrosis factor (TNF) inhibitors because of their ability to reactivate latent tuberculosis and particularly infliximab because of the development of drug antibodies. If psoriasis is not adequately controlled by these treatments, people may receive second-line biological treatments, which they continue to receive as long as the drugs continue to work. In addition, the Committee heard that treatment with etanercept (which may be given continuously or intermittently) is offered continuously, rather than intermittently. The clinical experts informed the Committee that, if the disease no longer responds to 1 biological treatment, they offer patients another. This pattern is

likely to be repeated over a patient's lifetime; clinical experts noted therefore that it is valuable to have a range of biological treatment options with different mechanisms of action available. The clinical experts noted the large positive impact that biological treatments have had on patients over the recent years because patients no longer need to be hospitalised for long periods to receive treatment or monitoring. The clinical experts stated that, because of this, fewer dedicated hospital beds for psoriasis now exist. With respect to secukinumab, the clinical experts stated that they were unlikely to choose it first from among the biological treatments because its long-term adverse-effects profile and real-world effectiveness were not yet well established. The Committee agreed that patients and clinicians value biological treatments such as secukinumab, and that biological treatments administered continuously would be given in clinical practice to the population defined in the scope for this appraisal. It therefore agreed that biological treatments were the most appropriate comparators for secukinumab.

- 4.3 The Committee heard from the clinical experts that clinicians use both the Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) when monitoring disease and choosing who to offer biological therapies to. This is because of the requirements outlined in existing NICE guidance for biological treatments, and that 'severe' disease is defined as a PASI of 10 or more, and a DLQI of more than 10. However, the Committee also heard that these measures do not identify everyone who might benefit from treatment, for example, people with limited disease but in high impact areas (such as the hands, feet and genitals), or people with anxiety and depression because of their condition. The Committee concluded that PASI and DLQI, which reflect the outcomes used in the trials, are relevant measures used in clinical practice in the NHS.

Clinical effectiveness

- 4.4 The Committee considered the clinical trials identified in the company submission, agreeing that the company had included relevant, high-quality trials which contained comparisons with both placebo and an active comparator. It concluded that the clinical trial evidence was appropriate for decision making.
- 4.5 The Committee considered the baseline characteristics of the patients in the trials and heard from clinical experts that they broadly reflected the UK population with severe psoriasis. The Committee noted that the population in the trials and the marketing authorisation for secukinumab included people who are candidates for 'systemic therapy', which is defined as including both non-biological and biological treatments. Therefore, both the trials and marketing authorisation included some patients who had never received systemic or biological treatments, whereas the scope for this appraisal was narrower ('people for whom systemic treatments are not tolerated, not effective or contraindicated'). The clinical experts agreed with the company that, in clinical practice, secukinumab would be offered at the same time as the existing biological treatments rather than before. Because the results of the trials reflected the effectiveness of secukinumab in a population including people who had not previously received systemic treatments, the Committee was concerned about the extent to which prior systemic treatment could impact the clinical-effectiveness results of secukinumab. It heard from clinical experts that they did not expect prior systemic treatments to modify the effectiveness of secukinumab. With respect to prior biological treatments, most of which are TNF-alpha inhibitors, the clinical experts noted that, because secukinumab has a different mechanism of action, they did not expect a change in effectiveness; in general, they were not aware of any evidence that

prior treatment impacts the clinical effectiveness of current treatment. However, the Committee concluded that that it would have been more appropriate to present the results of an analysis excluding patients who had never received systemic therapies in line with the population in for which it was proposed to be used. Overall, the Committee concluded that, although the populations in the scope and trial differed, the results of the clinical trials were likely to be generalisable to patients with severe psoriasis and were appropriate for decision-making on the clinical effectiveness of secukinumab.

4.6 The Committee considered the relevance of the main outcomes used in the trials (that is, percentage reduction in PASI score), to clinical practice. The Committee debated whether measuring an improvement in PASI was objective; it heard from the clinical experts that, once experienced, clinicians can do a PASI assessment quickly with little variability between clinicians. For PASI 75, the primary outcome in the trials, the Committee agreed that this demonstrated whether treatments for psoriasis had a high level of effectiveness. However, even with outcomes such as PASI 75, the psoriasis that remains could still have a significant impact on quality of life, and therefore patients value any treatment that could completely clear the disease (that is, PASI 100). The Committee concluded that PASI 75 was a clinically relevant definition of response to treatment and that, in addition, complete clearance was important; therefore the evidence for PASI 100 should be taken into account when deciding the value of secukinumab to the NHS.

4.7 The Committee discussed the results of the clinical trials. It noted that the clinical trial evidence for secukinumab had generated statistically significant differences in the co-primary outcomes when compared with both placebo and etanercept (an active comparator

that is already recommended by NICE for the population covered by this appraisal). It further noted that a PASI 100 response (that is, complete clearance of disease), occurred more often with secukinumab than with either placebo or etanercept, and that complete clearance of disease was the most important outcome for patients (see sections 4.2 and 4.6). The Committee heard from the clinical experts that the effectiveness of secukinumab and other biologicals is likely to be lower in clinical practice than in the trials, in part, because trials may not include patients with refractory disease. The clinical experts considered treatment with secukinumab to represent a step-change in the management of psoriasis because it appears to clear disease in some patients, offers a different mechanism of action compared with the TNF-alpha inhibitors and ustekinumab, and is associated with a low risk of adverse events. The Committee concluded that the evidence had shown that secukinumab was clinically superior to both placebo and etanercept for all primary and secondary outcomes.

- 4.8 The Committee considered the network meta-analysis presented by the company to compare secukinumab with the other biological agents specified in the scope. The Committee considered potential limitations of the network meta-analysis which did not address possible heterogeneity of the patients involved in the trials (for example, prior treatments received). However, it noted that the secukinumab trial populations were likely to be similar with respect to heterogeneity to the trials to which they were being compared, and which formed the basis for previous NICE guidance. The Committee noted that the difference in effectiveness between secukinumab and etanercept was smaller in the direct trial evidence than it was in the network meta-analysis, which the company used for its modelling (see section 3.6 and table 3). The Committee further noted that, although the results of the network

meta-analysis suggested that secukinumab appears to be more clinically effective than etanercept and adalimumab, and to have similar clinical effectiveness to ustekinumab and infliximab, the only direct trial evidence was for secukinumab compared with etanercept. Therefore the Committee considered that the relative clinical effectiveness of biological treatments for all outcomes was unknown. The Committee was also concerned about the effectiveness of best supportive care generated by the network meta-analysis reflected, which appeared very low with only 3.6% of people randomised to best supportive care having a PASI 75 response. It heard from clinicians that, in clinical practice, the proportion of people with a PASI 75 response following treatment with best supportive care was likely to be substantially higher (possibly up to 60%) because best supportive care involves active treatments such as topical therapies, ciclosporin and phototherapy. However, the clinical experts stated that a response with best supportive care would be accompanied by disutility because of the intensive time-consuming, inconvenient and unpleasant treatments, and with patients relapsing sooner than with biologicals. Overall, the Committee agreed that there were a number of scenarios it would like to have seen presented in the company submission, including a network meta-analysis for additional outcomes such as utility values, and the impact of prior treatment, to help provide additional assurances about the robustness of the efficacy assumptions. However, it concluded that, despite the limitations of the network meta-analysis, it was sufficient for the purposes of decision-making.

- 4.9 The Committee discussed whether there were any relevant subgroups in which secukinumab might be more effective than in the overall population included in the trials, or which have more to gain. The Committee reflected that it would have liked to have seen

more analyses using patient-level data for people who have previously received either systemic non-biological or biological treatments, to help reduce any uncertainty about the extent to which prior treatment affects clinical effectiveness. The Committee further heard from the clinical experts that people with concomitant psoriatic arthritis were an important subgroup, particularly those with psoriatic arthritis affecting joints of the hand which could cause difficulty with self-injecting. The Committee was aware that the monthly administration of secukinumab would be easier to manage for these patients than of other biological agents that need to be injected more frequently. The Committee noted that the company was applying for a marketing authorisation for secukinumab for psoriatic arthritis, that this was being considered for appraisal by NICE, and that ideally 1 treatment would be given for both conditions. In addition, the Committee was aware that there may be small subgroups of patients with comorbidities in whom TNF-alpha inhibitors would be contraindicated (such as people with demyelinating diseases and heart failure) and for whom treatment with secukinumab would be preferred. The Committee discussed whether observational data exists, and learned of a UK registry for biologicals; the company informed the Committee that it did not have access to this registry. The Committee concluded that future appraisals would benefit from UK observational data, but at present there were not sufficient data to identify differential efficacy between people who had received different prior treatments.

- 4.10 The Committee discussed the adverse events associated with secukinumab, noting that it was generally tolerated, and that the events were consistent between the placebo, etanercept, and secukinumab 300 mg and 150 mg arms of the trials. The Committee was aware that, over time, real-world data on adverse events will accumulate. Given the evidence to date, the Committee

concluded that secukinumab did not appear to be associated with adverse events not already known for biological treatments in general.

Cost effectiveness

4.11 The Committee considered the company's health economic model and noted that the structure of the model was similar to previous appraisals for psoriasis, but did not represent established clinical practice for managing severe psoriasis in several ways including:

- patients with psoriasis would likely be treated with a series of biologicals, rather than with a single biological drug before moving on to best supportive care (see section 4.2)
- the 10-year time horizon was too short because psoriasis is a lifelong condition.

The Committee further considered that best supportive care is only a relevant comparator for people in whom all other biological treatments were either contraindicated or whose disease had not adequately responded to treatment. The Committee agreed that the short time horizon probably led to overestimated incremental cost effectiveness ratios (ICERs) because secukinumab delayed progression to more expensive, less effective best supportive care treatments. Overall, the Committee concluded that the structure of the model did not reflect UK clinical practice, which led to uncertainty about the cost-effectiveness estimates generated.

4.12 The Committee considered the sources used by the company to estimate resource use and costs associated with best supportive care, noting that the model was highly sensitive to these inputs, and specifically whether assumptions were taken from Fonia et al. (2010; the Evidence Review Group [(ERG] base case) or NICE's [psoriasis](#) guideline and hospital episode statistics (HES) data (the company base case). The Committee noted that, in both instances,

the resource use estimates of best supportive care were likely to overestimate actual current best supportive care. This is in part because the populations described in Fonia et al. and the costing template for NICE's [psoriasis](#) guideline differed from the population in this appraisal; the costing template for NICE's [psoriasis](#) guideline was for a specific, high-need subpopulation with very severe psoriasis, and Fonia et al. describes care in a tertiary care centre known for treating the most severely affected patients. The Committee further noted that HES data (used to inform length of stay in the base case) were not specifically only for people receiving treatment for psoriasis nor did they necessarily show the number of individual patients who were admitted. The Committee also heard from the clinical experts that, in recent years, the number of patients hospitalised for severe psoriasis has fallen (see section 4.2) because of the availability of a wider range of biological treatment options; therefore, overall hospitalisation costs associated with psoriasis have fallen. The Committee considered that neither the resource use from Fonia et al. nor from NICE's [psoriasis](#) guideline and HES data were plausible for the population with severe psoriasis. However, it concluded that resource use for best supportive care is closer to Fonia et al. than to the company's estimates, and that future appraisals for psoriasis should take into account the changes in relevant costs that have occurred over time. The Committee further concluded that defining costs associated with psoriasis was an area of high priority for research.

- 4.13 The Committee considered the assumption in the company's model that people who receive subcutaneous biological treatments are able to self-administer treatments after 1 hour of training. It noted that the ERG considered this unrealistic because a proportion of people would not be able to self-administer treatment (for example, because of physical disability or needle-phobia), and that a more

realistic training time estimate would be closer to 3 hours. It heard from clinical experts that most people would be competent at self-administration after 2 hours of training. However, most training sessions would take place during normal clinical visits, and so self-administration training was a cost that did not necessarily need to be separately modelled. Further, the clinical experts stated that the proportion unable to self-administer treatments subcutaneously would be small. The Committee noted that the ERG base cases included 3 hours of training rather than 1 hour, and the company was happy with this change, which did not have a large impact on cost-effectiveness estimates. The Committee concluded that it was clinically plausible to assume that most people could self-administer subcutaneous biological treatments, and that it was appropriate to model training costs using a time of 1–3 hours.

4.14 The Committee considered the company's assumption that modelled patients after treatment during the induction period remain in the same health state for the duration of treatment. It noted clinical data from the FIXTURE trial that showed that some people who were in the PASI 50–74 health state at 12 weeks got better, while others got worse over the remaining 52-week time period of the model. However the Committee heard from clinical experts that, in clinical practice, with some exceptions, the health state of most people with psoriasis generally remained stable after the induction period. This reassured the Committee that it was reasonable to assume in the model that people remain in the same health state.

4.15 The Committee discussed the validity of the clinical-effectiveness data from the network meta-analysis used by the company in its model. It was aware that registry data exist in the UK, but was not provided in the company's submission because the company stated it did not have access to the data. The Committee agreed

that these registry data was a rich source of information about the treatment of people with psoriasis and was disappointed that the company did not have access to these data. The Committee was concerned about the implausibly low value of 3.6% for the proportion of patients whose disease responds to best supportive care treatment (see section 4.8). The Committee noted that the population generating the clinical data underpinning the model had an average PASI higher than 20, which it understood reflected very severe psoriasis, therefore the response rates from the trials may be more relevant for people with very severe disease. The Committee concluded that, in the absence of 'real life' data on the response rates for secukinumab compared with other treatments, the network meta-analysis assumptions were appropriate to use. However, it concluded that the issues with the network meta-analysis added to the uncertainty in the cost-effectiveness estimates generated by the model.

4.16 The Committee considered the company's modelling assumption that 20% of all patients stop biological treatments each year, an assumption the company based on previous appraisals. The Committee heard from clinical experts that this rate was likely to be an overestimate because clinicians had an increasing number of treatments from which to choose. The Committee concluded that fewer patients stopped biologicals than had been assumed by the company but that, because this affected all biological treatments equally, this was likely to have a minimal effect on the cost effectiveness of secukinumab.

4.17 The Committee considered the quality of life and utility values used by the company in its model. It welcomed the use of utility values from trial data (in accordance with the guide to the methods of technology appraisals). However, it noted that the company had used a regression analysis (taking into account PASI and DLQI

scores) to predict the utility values in the model. The Committee agreed it that would have preferred to have seen the unadjusted EQ-5D utility values used in the model. The Committee discussed the plausibility of the absolute values used by the company, agreeing that the baseline utility value (0.642) seemed plausible, although the quality-adjusted life year (QALY) gain with biological treatments appeared to be low. The Committee noted this may have been because the model did not assume a survival benefit associated with treatment. The Committee noted that the model did not take into account the disutility values associated with best supportive care, and the added benefit of obtaining a complete remission with secukinumab (PASI 100), an important outcome for patients. The Committee concluded that the utility gains estimated from the model were likely to be underestimated.

4.18 The Committee discussed whether secukinumab could be considered innovative. It noted that secukinumab offers a different mechanism of action to the other biological treatments recommended by NICE, and some patients experience complete clearance of disease. The Committee also heard from clinical and patient experts that severe psoriasis can be associated with a stigma apart from its effect on health-related quality of life, and that NICE methods acknowledge giving extra weight to such conditions. Further, the Committee noted that the disutility of best supportive care was not included in the model. The Committee agreed that these benefits had not been captured when calculating the QALY, that secukinumab reflected a step change in treatment and that the drug could be considered innovative.

4.19 The Committee discussed the estimate of cost effectiveness based on the incremental analyses presented by the company. It noted that the ICERs were sensitive to the costs of best supportive care and the cost of secukinumab, and less sensitive to utility values or

assumed rates of stopping biological treatment. However, the Committee considered there to be significant structural and parameter uncertainties in the way that the treatment of psoriasis had been modelled, including: the short time horizon; the assumption that people receive only 1 treatment before best supportive care; and the low effectiveness of best supportive care. It further noted that, because the changes in incremental health benefits between different biological treatments were small, the ICERs could vary dramatically with small QALY changes. The Committee concluded that these structural and parameter uncertainties and the labile nature of the ICERs made it difficult to determine a precise cost-effectiveness estimate.

- 4.20 The Committee discussed whether it could determine a most plausible ICER, but agreed this was difficult because of the previously mentioned structural and parameter uncertainties in the model. The Committee and the company both agreed with the ERG's corrections to the model. The Committee also agreed that the most plausible assumptions on resource use were closer to Fonia et al. (2010; ERG base case) than to NICE's [psoriasis](#) guideline (company base case). Furthermore, the Committee considered that the ICERs compared with the biological treatments rather than with best supportive care were most appropriate. It agreed that the ICERs ranging from approximately £17,700 per QALY gained (compared with ustekinumab 90 mg) to £42,400 per QALY gained (compared with etanercept) were probably overestimated because the model had not accounted for PASI 100 responses (see section 4.17) nor the disutility values associated with best supportive care. In addition, the Committee pragmatically considered the cost effectiveness of secukinumab in the light of previous appraisals in this disease area. The Committee noted that, even when using direct trial data, secukinumab was more effective

than at least one of the already recommended biologicals, etanercept, and was associated with a higher probability of complete remission. Considering the patient access scheme price of secukinumab, the clinical data (compared with etanercept in the FIXTURE trial and with the results of the network meta-analysis), and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with the other biologicals already recommended in previous NICE guidance. The Committee therefore concluded that secukinumab could be recommended as a cost-effective use of NHS resources.

- 4.21 The Committee discussed the inclusion of a stopping rule in the recommendation. When discussing the appropriate time point at which to measure response, it noted that the trials and the model assessed the effectiveness of secukinumab for the primary outcome at week 12. The Committee was aware that because the clinical effectiveness of secukinumab continued beyond 12 weeks (with a peak effect at week 16), the summary of product characteristics notes that consideration should be given to stopping treatment in people who have not shown a response up to week 16. However, the Committee noted that there is no appropriate placebo data with which to compare the clinical effectiveness of secukinumab at 16 weeks because patients in the placebo arm of the trials were able to crossover to active treatment if they did not have a response at week 12. Also, the company base case used a 12 week stopping rule. The Committee considered the relevance of stopping rules in existing NICE guidance for biologicals for treating severe psoriasis that, in addition to the PASI 75 response, also refers to a PASI 50 response with a 5-point reduction in DLQI from the start of treatment. The Committee considered that, because secukinumab was likely to be given at the same point in the pathway as the other

biologicals already recommended by NICE for treating psoriasis, any stopping rules should be consistent with previous appraisals. The Committee concluded that the most appropriate time point to assess response was week 12, and that the outcomes used to assess response should be consistent with previous appraisals for psoriasis.

- 4.22 The Committee was aware that there might be some situations when the DLQI may not be a clinically appropriate tool to inform a clinician's conclusion about the severity of psoriasis; for example, if a person has physical, sensory or learning disabilities, or communication difficulties that could affect their responses to the questionnaire. The Committee heard from the clinical specialists that the DLQI is now available in more than 50 languages and that this has improved assessment for those people whose first language is not English. The Committee concluded that healthcare professionals should take any physical, sensory or learning disabilities and communication difficulties into account when using the DLQI and make any adjustments they consider appropriate.
- 4.23 The Committee considered a potential equality issue raised by a patient organisation that people with psoriatic arthritis affecting their fingers could find using the pre-filled syringe difficult, as could those with a needle phobia. The Committee had already concluded that the monthly administration of secukinumab would be easier to manage for these patients than of other biological agents that need to be injected more frequently (see section 4.9). Bearing in mind that the Committee had recommended secukinumab (see section 4.20), it concluded that there was no need to alter or add to its recommendations. It also noted that a separate appraisal was being considered for secukinumab for people with psoriatic arthritis.

4.24 The Appraisal Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising secukinumab. The Appraisal Committee noted NICE’s position statement in this regard, and accepted the conclusion “that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines”. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of secukinumab. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of cost effectiveness of secukinumab.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Secukinumab for treating moderate to severe plaque psoriasis	Section
Key conclusion		
Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when: <ul style="list-style-type: none"> • the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 • the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them 		1.1

<ul style="list-style-type: none"> the company provides secukinumab with the discount agreed in the patient access scheme. <p>The Committee concluded that the clinical evidence had shown that secukinumab was clinically superior to both placebo and etanercept for all primary and secondary outcomes.</p> <p>The Committee agreed that it was difficult determine a most plausible incremental cost-effectiveness ratio (ICER) because of the structural and parameter uncertainties in the model. It agreed that the ICERs ranging from approximately £17,700 per QALY gained (compared with ustekinumab 90 mg) to £42,400 per QALY gained (compared with etanercept) were probably overestimated because the model had not accounted for PASI 100 responses nor the disutility values associated with best supportive care. Considering the patient access scheme price of secukinumab, the clinical data, and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with the other biologicals already recommended in previous NICE guidance.</p>	<p>4.7</p> <p>4.11</p> <p>4.15</p> <p>4.19</p> <p>4.20</p>	
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the patient and clinical experts that psoriasis can be physically and psychologically debilitating, particularly if located on the hands, feet and genitals. The Committee heard that, because psoriasis is visible, it can make people feel isolated and lonely, which could lead to them losing self-confidence and avoiding social situations, and could affect career opportunities and influence intimate relationships. The clinical experts informed the</p>	<p>4.1</p> <p>4.2</p>

	<p>Committee that, if the disease no longer responds to treatment with 1 biological, they offer patients another biological. This pattern is likely to be repeated over a patient's lifetime; clinical experts noted that it is therefore valuable to have a range of biological treatment options with different mechanisms of action available.</p>	
The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee noted that secukinumab offers a different mechanism of action to the other NICE-recommended biological treatments, and some patients experience complete clearance of disease. The Committee also heard from clinical and patient experts that severe psoriasis can be associated with a stigma, apart from its effect on health-related quality of life, and that NICE methods acknowledge giving extra weight to such conditions. The Committee agreed that these benefits had not been captured when calculating the quality-adjusted life years (QALYs), that secukinumab reflected a step change in treatment and that the drug could be considered innovative.</p>	<p>4.18</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee heard from the clinical experts that, if psoriasis is not adequately controlled by first-line treatments including topical treatments, systemic non-biological therapies (such as methotrexate) and phototherapy, people may receive second-line biological treatments, which they continue to receive as long as the drugs continue to work. If the disease no longer responds to treatment with 1 biological, clinicians offer patients another biological. The Committee agreed that biological treatments were the most appropriate comparators for secukinumab.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The Committee concluded that secukinumab did not appear to be associated with adverse events not already known for biological treatments in general.</p>	<p>4.9</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The company included 5 relevant international, multicentre, phase 3, double-blind, randomised, controlled trials. The Committee agreed that the company had included relevant, high-quality trials.</p> <p>The Committee considered that the network meta-analysis excluded outcomes other than effectiveness, such as utility values, and did not address possible heterogeneity of the patients involved in the trials (for example, prior treatments received). However, it noted</p>	<p>3.1 4.4 4.8</p>

	<p>that the secukinumab trial populations were likely to be similar with respect to heterogeneity to the trials to which they were being compared, and which formed the basis for previous NICE guidance. The network meta-analysis also generated a low value of people who achieved PASI 75 (3.6%). Overall, the Committee agreed that, despite the limitations of the network meta-analysis, it was sufficient for the purposes of decision-making.</p>	
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee noted that, although both the trials and marketing authorisation included some patients who had never received systemic or biological treatments compared with the scope ('people for whom systemic treatments are not tolerated, not effective or contraindicated'), in clinical practice, secukinumab would be offered at the same time as the existing biological treatments. The Committee considered that the baseline characteristics of the patients in the trials broadly reflected the UK population with severe psoriasis. The Committee concluded that, although the populations in the scope and trial differed, the results of the clinical trials were likely to be generalisable to patients with severe psoriasis and were appropriate for decision-making on the clinical effectiveness of secukinumab.</p>	<p>4.5</p>

<p>Uncertainties generated by the evidence</p>	<p>The people enrolled in the clinical trials included some patients who had never received systemic or biological treatments. The Committee reflected that it would have liked to have seen more analyses using patient-level data for people who have previously received either systemic non-biological or biological treatments, to help reduce any uncertainty about the extent to which prior treatment affects clinical effectiveness.</p> <p>The Committee agreed that there were a number of scenarios it would like to have seen presented in the main submission (including a network meta-analysis for additional outcomes such as utility values and the impact of prior treatment) to help provide additional assurances about the robustness of the efficacy assumptions of the network meta-analysis.</p>	<p>4.5 4.9</p>
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<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee heard from the clinical experts that people with concomitant psoriatic arthritis were an important subgroup, and that ideally 1 treatment would be given for both conditions; the Committee noted that the company was applying for a licence for secukinumab for psoriatic arthritis, and this was being considered for appraisal by NICE.</p> <p>It also further noted that there may be small subgroups of patients with co-morbidities in whom TNF-alpha inhibitors would be contraindicated (such as people with demyelination and heart failure) and for whom treatment with secukinumab would be preferred.</p>	<p>4.9</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee agreed that secukinumab was clinically superior to both placebo and etanercept for all primary and secondary outcomes.</p>	<p>4.7</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company constructed a new economic model with a 10-year time horizon (1-year decision tree and 9-year Markov cohort model) to compare secukinumab 300 mg with etanercept, ustekinumab (45 mg and 90 mg), adalimumab, infliximab and best supportive care.</p>	<p>3.18</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee concluded that the structure of the model did not reflect UK clinical practice (because patients did not receive subsequent biological treatments and the time horizon of 10 years was too short), which led to uncertainty about the robustness of the cost-effectiveness estimates generated.</p> <p>The Committee concluded that the issues with the network meta-analysis added to the uncertainty in the cost-effectiveness estimates generated by the model.</p>	<p>4.11</p> <p>4.15</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee agreed that the baseline utility value of 0.642 seemed plausible, although the QALY gain with biological treatments appeared to be low. The Committee noted that the model did not take into account the disutility values associated with best supportive care, and the added benefit of obtaining a complete remission with secukinumab (PASI 100). The Committee concluded that the utility gains estimated from the model were likely to be underestimated.</p> <p>The Committee also heard from clinical and patient experts that severe psoriasis can be associated with a stigma apart from its effect on health-related quality of life, and that NICE methods acknowledge giving extra weight to such conditions.</p>	<p>4.17</p> <p>4.18</p>

<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee concluded that, at present, there were not sufficient data to identify differential efficacy between people who had received different prior treatments.</p>	<p>4.9</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee noted that the model was highly sensitive to the costs assumed for best supportive care, and specifically whether assumptions were taken from Fonia et al. (2010; the ERG base case) or NICE's psoriasis guideline and hospital episode statistics (HES) data (the company base case). It further noted that, because the changes in incremental health benefits between different biological treatments were small, the ICERs could vary dramatically with small QALY changes.</p>	<p>4.12 4.19</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered there to be significant structural and parameter uncertainties in all of the incremental analyses, including: the short time horizon; the assumption that people receive only 1 treatment before best supportive care; and the low effectiveness of best supportive care.</p> <p>The Committee considered that the ICERs compared with the biological treatments ranged from approximately £17,700 per QALY gained (compared with ustekinumab 90 mg) to £42,400 per QALY gained (compared with etanercept). The Committee concluded that these ICERs were probably overestimated because of the short time horizon, and because the model had not accounted for PASI 100 responses nor the disutility values associated with best supportive care.</p> <p>Considering the patient access scheme price of secukinumab, the clinical data, and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with the other biologicals already recommended in previous NICE guidance.</p>	<p>4.20</p>
<p>Additional factors taken into account</p>		

Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial-in-confidence.	2.3
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	A patient organisation expressed the view that people with psoriatic arthritis affecting their fingers could find using the pre-filled syringe difficult, as could those with a needle phobia. The Committee concluded that the monthly administration of secukinumab would be easier to manage for these patients than of other biological agents that need to be injected more frequently. Bearing in mind that the Committee had recommended secukinumab, it concluded that there was no need to alter or add to its recommendations. .	4.9 4.22

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the

recommendations in this appraisal within 3 months of its date of publication.

- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has psoriasis and the doctor responsible for their care thinks that secukinumab is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 5.4 The Department of Health and Novartis have agreed that secukinumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]
- 5.5 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]
- Slides highlighting key messages for local discussion.
 - Costing template and report to estimate the national and local savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Psoriasis: the assessment and management of psoriasis](#). NICE clinical guideline 153 (2012)
- [Ustekinumab for the treatment of adults with moderate to severe psoriasis](#). NICE technology appraisal guidance 180 (2009)
- [Adalimumab for the treatment of adults with psoriasis](#). NICE technology appraisal guidance 146 (2008)
- [Infliximab for the treatment of adults with psoriasis](#). NICE technology appraisal guidance 134 (2008)
- [Grenz rays therapy for inflammatory skin conditions](#). NICE interventional procedure guidance 236 (2007)
- [Etanercept and efalizumab for the treatment of adults with psoriasis](#). NICE technology appraisal guidance 103 (2006). Note: guidance for efalizumab has now been withdrawn.

Under development

Apremilast for treating moderate to severe psoriasis. NICE technology appraisal guidance, publication expected August 2015.

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
May 2015

8 Appraisal Committee members, guideline representatives and NICE project team

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Dr Neil Iosson

Locum General Practitioner

Dr Sanjay Kinra

Clinical Lecturer, University of Warwick

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne

Professorial Fellow in Public Health, Wessex Institute, University of Southampton

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Mr Cliff Snelling

Lay Member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Carl Prescott

Technical Lead

Eleanor Donegan

Technical Adviser

Jeremy Powell

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:

- Cummins E, Scott N, Cruickshank M et al, Secukinumab for treating moderate to severe plaque psoriasis, February 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Company

- Novartis

II. Professional/expert and patient/carer groups:

- British Association of Dermatologists
- British Dermatological Nursing Group
- Psoriasis Association
- Psoriasis and Psoriatic Arthritis Alliance
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- AbbVie

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Merck Sharp & Dohme
- Pfizer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on secukinumab by providing oral evidence to the Committee.

- Dr Ruth Murphy, nominated by British Association of Dermatologists - clinical expert
- Professor Catherine Smith, nominated by British Association of Dermatologists - clinical expert
- Lucy Moorhead, nominated by British Dermatological Nursing Group - clinical expert
- David Chandler, nominated by Psoriasis and Psoriatic Arthritis Alliance - patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis