Apremilast for treating moderate to severe plaque psoriasis

Technology appraisal guidance
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Contents

1 Guidance ............................................................................................................................................................................ 3
2 The technology .................................................................................................................................................................... 4
3 The company's submission ............................................................................................................................................. 5
   Clinical effectiveness ............................................................................................................................................................ 5
   Cost effectiveness ................................................................................................................................................................. 11
   Additional analyses submitted by the company .................................................................................................................. 19
4 Consideration of the evidence .......................................................................................................................................... 22
   Clinical management ........................................................................................................................................................... 22
   Clinical effectiveness ............................................................................................................................................................ 24
   Cost effectiveness ................................................................................................................................................................. 27
   Summary of Appraisal Committee's key conclusions ..................................................................................................... 35
5 Review of guidance ............................................................................................................................................................ 41
6 Appraisal Committee members, guideline representatives and NICE project team ............................................ 42
   Appraisal Committee members ........................................................................................................................................ 42
   NICE project team ............................................................................................................................................................. 44
7 Sources of evidence considered by the Committee ....................................................................................................... 45
About this guidance............................................................................................................................................................... 47
1 Guidance

1.1 Apremilast is not recommended within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated.

1.2 People whose treatment with apremilast was funded by the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
2 The technology

2.1 Apremilast (Otezla, Celgene) is a small-molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast down-regulates the inflammatory response by modulating the expression of cytokines and mediators associated with psoriasis (including tumour necrosis factor [TNF]-alpha and interleukin [IL]-23). Apremilast has a marketing authorisation in the UK ‘for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including [ciclosporin], methotrexate or psoralen and ultraviolet-A light (PUVA)’.

2.2 The summary of product characteristics includes the following adverse reactions for apremilast: gastrointestinal disorders (most commonly diarrhoea and nausea), upper respiratory tract infections, headache and tension headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Apremilast is administered orally. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10-mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule). The price of apremilast is £265.18 for a 14-day treatment initiation pack (4×10 mg, 4×20 mg, 19×30 mg) and £550.00 for a 28-day pack (56×30 mg tablets) (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] online, accessed March 2015). According to the company submission, the cost of 18 months of treatment with apremilast is estimated at £10,644. Costs may vary in different settings because of negotiated procurement discounts.
3 The company's submission

The Appraisal Committee (section 6) considered evidence submitted by Celgene and a review of this submission by the Evidence Review Group (ERG; section 7).

Clinical effectiveness

3.1 The clinical evidence for apremilast came from 4 multicentre, placebo-controlled, double-blind randomised controlled trials (RCTs) in people with moderate to severe chronic plaque psoriasis:

- PSOR-005 (n=352): a phase IIb trial across 35 sites in the USA and Canada.
- PSOR-008 (also called ESTEEM 1, n=844): a phase III trial across 72 sites in 8 countries (including the UK).
- PSOR-009 (also called ESTEEM 2, n=411): a phase III trial across 45 sites in 9 countries (not including the UK).
- PSOR-010 (n=250): a phase IIIb trial across 65 sites in 11 countries (including the UK).

The primary endpoint in all 4 trials was a 75% reduction in the Psoriasis Area Severity Index (PASI) score at week 16 (known as a PASI 75 response).

3.2 PSOR-005 was a 24-week trial of apremilast compared with placebo. People with moderate to severe psoriasis were randomised 1:1:1:1 to placebo or apremilast at 1 of 3 different doses (10 mg, 20 mg or 30 mg twice daily). At week 16, people receiving placebo were re-randomised to apremilast 20 mg or 30 mg for a further 8 weeks; people receiving apremilast continued with their allocated treatment.

3.3 In PSOR-008 and PSOR-009, people were randomised (2:1) to apremilast 30 mg (twice daily) or placebo. The PSOR-010 trial was powered to compare apremilast with placebo, and etanercept with placebo. People were randomised 1:1:1 to placebo (tablet and injection), apremilast (30 mg twice daily) plus placebo injections, or etanercept (50 mg injection once weekly) plus placebo tablets. In all 3 trials, moderate to severe plaque psoriasis was defined by a PASI score of at least 12, 10% or more of body surface area affected, and a static Physician Global Assessment score (sPGA) of at least 3. There was no requirement for people to have a particular Dermatology Life Quality Index.
(DLQI) score at baseline. The studies excluded people with tuberculosis, HIV and hepatitis. PSOR-010 also excluded patients with prior use of biological therapies (for treating psoriatic arthritis or psoriasis).

3.4 PSOR-008 and PSOR-009 each had 4 treatment phases with a planned overall duration of 5 years:

- Placebo-controlled phase (weeks 0–16): patients were randomised to have apremilast or placebo in a 2:1 ratio.

- Maintenance phase (weeks 16–32): patients randomised to placebo were switched to apremilast.

- Treatment withdrawal phase (weeks 32–52) to assess whether the effect of treatment continues (or decreases) after stopping apremilast:
  - Patients originally randomised to apremilast whose disease responded to treatment were randomised again (1:1) to apremilast or placebo; patients randomised to placebo at 32 weeks were switched back to apremilast if the response was lost.
  - Patients originally randomised to apremilast whose disease did not respond remained on apremilast and could additionally have topical therapies and/or phototherapy.
  - All patients originally randomised to placebo (and switched to apremilast at week 16) remained on apremilast, and those whose psoriasis had not responded by week 32 could additionally have topical therapies and/or phototherapy.

- Long-term extension (weeks 52–260; data available up to week 104 for PSOR-008 and week 52 for PSOR-009).

All efficacy and safety outcomes assessed during the placebo-controlled phase (weeks 0–16) were also measured during the maintenance phase and treatment withdrawal phase. The long-term extension phase is continuing to collect the same data. Blinding was maintained until all patients completed week 52. The main difference in design between the PSOR 008 and PSOR 009 was the definition of response to treatment to determine whether patients continued treatment after 32 weeks: PASI 75 in PSOR 008 and PASI 50 in PSOR 009.
3.5 PSOR-010 had 2 treatment phases with a planned overall duration of 104 weeks. At week 16, all patients who had previously not received apremilast were switched to apremilast for the 88-week extension phase of the trial. The ongoing long-term extension phase is continuing to collect the same efficacy and safety outcomes as the placebo-controlled phase.

3.6 The company considered the baseline characteristics of patients to be similar between PSOR-008 and PSOR-009, and similar between the treatment groups within the trials. In PSOR-010, a higher proportion of people had previously had conventional systemic therapy than in the other trials, and the proportion of patients with a 'severe' score on the PGA was lower (15.7–27.4% across the treatment groups) than in the other trials (27.4–35.8%). Mean PASI score ranged from 18.7 to 20.3 across the 3 phase III trials (PSOR-008, PSOR-009, PSOR-010), and mean DLQI score ranged from 12.1 to 12.8.

3.7 The results for key outcomes in the 2 pivotal phase III trials (PSOR-008 and PSOR-009) are presented in table 1. The company provided results from PSOR-010 as 'academic in confidence'. After 16 weeks of treatment in PSOR-010, a statistically significantly greater proportion of people treated with apremilast achieved a PASI 75, PASI 50 or PASI 90 response, or an sPGA score of clear or almost clear with a 2 or more unit change from baseline, compared with placebo.

Table 1 Key outcomes in the PSOR-008 and PSOR-009 clinical trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PSOR-008</th>
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<th>PSOR-009</th>
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<tr>
<td></td>
<td>16 weeks</td>
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<td>APR</td>
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<tr>
<td>(n=562)</td>
<td>(n=562)</td>
<td>(n=274)</td>
<td>(n=274)</td>
<td>(n=137)</td>
<td>(n=274)</td>
<td>(n=274)</td>
</tr>
<tr>
<td>PASI 75, %</td>
<td>33.1*</td>
<td>5.3</td>
<td>28.3</td>
<td>28.8*</td>
<td>5.8</td>
<td>24.8</td>
</tr>
<tr>
<td>sPGA score 0 or 1, %</td>
<td>21.7*</td>
<td>3.9</td>
<td>24.0</td>
<td>20.4*</td>
<td>4.4</td>
<td>17.9</td>
</tr>
<tr>
<td>PASI 50, %</td>
<td>58.7*</td>
<td>17.0</td>
<td>53.6</td>
<td>55.5*</td>
<td>19.7</td>
<td>46.0</td>
</tr>
<tr>
<td>PASI 90, %</td>
<td>9.8*</td>
<td>0.4</td>
<td>12.1</td>
<td>8.8†</td>
<td>1.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>
3.8 During the treatment withdrawal phase of PSOR-008 (weeks 32–52), several patients in the apremilast arm lost PASI 75 response (data marked as 'academic in confidence' by the company). After 104 weeks, 63.2% of the 844 patients who had had apremilast during the trial had stopped apremilast. The primary reasons for stopping apremilast were lack of efficacy (27.5%), withdrawal of consent by the patient (12.8%) and adverse events (9.5%).

3.9 Health-related quality of life in PSOR-008 and PSOR-009 was measured at baseline and again at 16 and 32 weeks after starting treatment. Health-related quality of life improved statistically significantly after 16 weeks of treatment with apremilast, and the improvement was sustained at 32 weeks (according to the 4 questionnaires used: DLQI, 36-item Short-Form Health Survey [SF-36], EQ-5D, 100 mm Pruritus Visual Analogue Scale [VAS]). People receiving apremilast in PSOR-010 also had statistically significantly improvements in mean change in DLQI score and mean change in pruritus VAS score after 16 weeks of treatment.

3.10 In an exploratory analysis of PSOR-008, a clinical benefit was seen with apremilast regardless of baseline DLQI score. Similar proportions of patients with a baseline DLQI of 10 or less or a DLQI of more than 10 achieved PASI 75 at week 16 with apremilast (33.5% and 32.9% respectively).

3.11 Pooled data from PSOR-008 and PSOR-009 showed that more patients receiving apremilast had at least 1 adverse event (68.9%) than people receiving placebo (57.2%) in the first 16 weeks of treatment. Adverse events occurring in 5% or more of either the apremilast or placebo treatment populations were diarrhoea (17.8% with apremilast and 6.7% with placebo), nausea (16.6% and 6.7%), upper respiratory tract infection (8.4% and 6.5%), tension headache (7.3% and 3.3%), nasopharyngitis (7.3% and 6.9%) and headache (5.8% and 3.3%). Few patients reported severe or serious adverse events during the placebo-controlled phase of the trials, and the incidence of severe or serious adverse events was similar for placebo and apremilast. Few patients stopped
therapy due to adverse events in the first 16 weeks of treatment (5.4% with apremilast, 3.8% with placebo). In the first 16 weeks of treatment in the PSOR-010 trial, more patients receiving apremilast had at least 1 adverse event (69.9%) compared with placebo (59.5%) or etanercept (53.0%) and the proportion of patients reporting a serious adverse event was higher in the apremilast group (3.6%) than the placebo (0%) or etanercept (1.2%) groups, although numbers were low.

3.12 Because PSOR-010 was not powered to compare apremilast with etanercept, and there were no other head-to-head trials comparing apremilast with any of the biological therapies currently recommended by NICE for psoriasis (adalimumab, etanercept, infliximab, secukinumab and ustekinumab), the company did a systematic review and network meta-analysis, which included 22 studies. This was subsequently updated to include outcomes from 2 additional studies (including PSOR-010, which was unavailable at the time of the company's original submission). All except 1 study included placebo as the control group (the other study investigated 2 different doses of ustekinumab). The company did a sensitivity analysis including the 17 trials that reported separate results for people who had not had biological therapy. The company reported that the probability of moderate to severe psoriasis responding was greatest for infliximab, followed by ustekinumab and adalimumab; etanercept had the lowest probability of a response among the biological therapies. Response rates with apremilast (marked as 'academic in confidence' by the company) were lower than for the biological therapies; this difference was statistically significant for comparisons with all biological therapies except with etanercept. The results of the company's sensitivity analysis in patients who had not had biological therapies were consistent with the base-case results for the overall population.

**ERG comments**

3.13 The ERG concluded that the trials were of good quality and that treatment groups were generally similar at baseline. The ERG noted that, although the follow-up period for PSOR-005 was relatively short (24 weeks), it was adequate for assessing the primary outcome of PASI 75 response at week 16.

3.14 The ERG suggested that the populations in the 4 trials of apremilast may not be representative of patients seen in clinical practice. All 4 trials excluded people
with a history of other clinically significant diseases (including cardiac, neurological, psychiatric, hepatic, renal, haematological and immunological disease), and PSOR-008, PSOR-009 and PSOR-010 excluded people with significant infection or a psoriasis flare or rebound within 4 weeks of screening. Not everyone in the PSOR-008 and PSOR-009 trials had systemic therapy or had disease that had not responded to systemic treatments, whereas the marketing authorisation for apremilast is in people whose disease has responded inadequately to, or who have a contraindication to or cannot tolerate, systemic therapies, including non-biological treatments and phototherapy. Less than half of people in PSOR-008 and PSOR-009 had conventional systemic therapy and only about 65% had any form of systemic therapy. Based on this, the ERG suggested that the PSOR-008 and PSOR-009 trials might have overestimated the clinical effectiveness of apremilast because people may have had less severe disease than those for whom apremilast would be considered in NHS practice. The ERG considered that the proportion of patients who had conventional systemic therapy in PSOR-010 better reflected patients seen in UK clinical practice.

3.15 The ERG noted that withdrawal rates were quite high and that treatment benefit was not fully maintained in a substantial proportion of patients (marked as 'academic in confidence' by the company).

3.16 Based on data from PSOR-008, a consistent beneficial treatment effect across all subgroups was seen with apremilast compared with placebo. However, the ERG suggested that only 13% of the PSOR-008 trial population would be eligible for apremilast based on the company's preferred positioning for apremilast in the treatment pathway (2 or more conventional systemic therapies failed or contraindicated and no previous biological therapy). For people whose psoriasis had not responded to at least 1 biological therapy, the ERG judged the sample size to be too small to inform the treatment effect of apremilast in this subgroup. In addition, the ERG suggested that this small subgroup of people who had used biological agents does not accurately reflect UK clinical practice because many of the people in the apremilast trials had biological therapies for psoriasis without first trying conventional systemic therapies.

3.17 For PSOR-010, the company did not submit results that directly compare apremilast with etanercept. The ERG calculated odds ratios (ORs), which
indicated that etanercept improved PASI response slightly more than apremilast (PASI 75: OR for etanercept 1.41, 95% confidence interval [CI] 0.76 to 2.61). The ERG noted that the trial was not powered to compare etanercept and apremilast, and therefore these results should be interpreted with caution.

3.18 The ERG stated that the company's network meta-analysis appeared to have included all trials relevant to the decision problem and that most of the 24 trials were rated good or excellent in quality. The ERG stated that the results from the company's network meta-analysis were likely to be reasonably reliable. However, the ERG said that, for people who never had biological therapies, the results of the company's sensitivity analysis should be interpreted with caution because:

- trials did not consistently report whether patients had biological therapy
- some data were based on people who did not have tumour necrosis factor-inhibitor therapy (adalimumab, etanercept or infliximab) but may have had other types of biological therapies, for example, those that target interleukins, such as ustekinumab
- some trials in the sensitivity analysis included a small number of patients (less than 20% of the trial population) who previously had biological therapies, whereas the sensitivity analysis was meant to include people who never had biological treatments.

3.19 The ERG noted that the company did not present any data on the response of psoriasis to biological therapies after treatment with apremilast. Therefore the ERG was unclear whether apremilast affects the effectiveness of subsequent biological therapies.

Cost effectiveness

3.20 The company provided a Markov state-transition cohort model over a 10-year time horizon, using a 28-day cycle length. All costs and outcomes were discounted by 3.5% and the company stated that costs were from the NHS and personal social services perspective.

3.21 The health states in the company's Markov model comprised a short-term 'trial period' to determine initial response rate, and a long-term 'continued response' period. Apremilast was modelled as an additional treatment in a sequence. In the apremilast treatment sequence, patients could move through a maximum of
3 lines of treatment in addition to apremilast. In the comparator sequence, patients moved through the same lines of therapy, but without apremilast. In the company’s base-case analysis, 2 different populations were modelled according to differences in DLQI score (both populations had the same PASI score). For people with a PASI score of at least 10 and a DLQI score of more than 10, the company compared a treatment sequence including apremilast (apremilast followed by 2 biological therapies and best supportive care) with a treatment sequence without apremilast (2 biological therapies and best supportive care). For people with a PASI score of at least 10 and a DLQI score of equal to or less than 10, the company compared a treatment sequence of apremilast followed by best supportive care with best supportive care alone. Patients who moved to best supportive care remained in this health state for the rest of the analysis (up to 10 years) or until they died. The company did not define best supportive care in its submission. The NICE psoriasis guideline defined it as a combination of systemic non-biological therapies, phototherapy and complex topical agents delivered in day-care settings and during inpatient stays.

3.22 The duration of the trial period in the model ranged from 10 to 16 weeks for biological therapies depending on the treatment (16 weeks for adalimumab or ustekinumab, 12 weeks for etanercept and 10 weeks for infliximab), based on current recommendations in the NICE guideline on psoriasis for assessing response with each treatment. The company used a 16-week trial period for apremilast because response to treatment was evaluated 16 weeks after starting apremilast in the phase 3 clinical trials (PSOR-008 and PSOR-009). In the base-case analysis, the company defined response to treatment at the end of the trial period as a 75% reduction in PASI score (PASI 75). Patients who had a PASI 75 response at the end of the trial period transitioned to the 'continued use' health state. The estimates of response to treatment in the model of people with a DLQI score of more than 10 were based on probabilities generated in the company's original base-case network meta-analysis (which did not include results from the PSOR-010 trial). For the analysis in people with a DLQI score of 10 or less, response to treatment was based on subpopulation results from the PSOR-008 and PSOR-009 trials. The probability of response for each treatment was assumed to be the same regardless of its point in the sequence. The company assumed that best supportive care provided no benefit.

3.23 To extrapolate data beyond the clinical trials, the company assumed that response rates (PASI 50, 75 and 90 rates) remain constant over time,
irrespective of patients’ ages and response to previous treatments. Patients in the model could die in any health state. In the company’s model, psoriasis did not affect the death rate.

3.24 The company assumed the same all-cause withdrawal probability for all biological therapies in the model (20%) and also for apremilast in the base case, in the absence of long-term withdrawal data.

3.25 Although the company collected EQ-5D scores at baseline and at 16 weeks in the clinical trials of apremilast, these data were not used in the base-case analysis for people with a DLQI score of more than 10 because EQ-5D scores were not available for all of the biological therapies included in the model. The company assigned utility values to each health state in the model based on the change in utility from baseline associated with the different PASI response categories reported in published literature (Woolacott et al. 2006), and the proportion of patients whose disease responded in each health state (see table 2). The utility values in Woolacott et al. had been estimated through mapping the DLQI associated with PASI responses from etanercept trials to changes in EQ-5D utility. However, for the analysis in people with a DLQI score of 10 or less, the company used EQ-5D data collected from PSOR-008 and PSOR-009. The company used the same baseline utility value (0.7; based on published data) in both analyses (DLQI more than 10 and DLQI 10 or less). The company assumed that best supportive care is not associated with any improvement in health-related quality of life.

Table 2 Health-related quality of life in the company model for DLQI more than 10 (data not reported for DLQI 10 or less model): changes in utility from baseline based on PASI response

<table>
<thead>
<tr>
<th>PASI response</th>
<th>Change in utility from baseline</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than PASI 90</td>
<td>0.21</td>
<td>0.11 to 0.31</td>
</tr>
<tr>
<td>PASI 90</td>
<td>0.19</td>
<td>0.11 to 0.27</td>
</tr>
<tr>
<td>PASI 75</td>
<td>0.17</td>
<td>0.09 to 0.25</td>
</tr>
<tr>
<td>Less than PASI 50</td>
<td>0.05</td>
<td>0.03 to 0.07</td>
</tr>
</tbody>
</table>

Abbreviation: PASI, Psoriasis Area Severity Index.
3.26 The company's model did not include administration costs associated with apremilast or other oral therapies (including ciclosporin and methotrexate) or subcutaneous injections (adalimumab, etanercept and ustekinumab) because these were all assumed to be self-administered. An administration cost was included for each infusion of infliximab, to cover inpatient hospitalisation. The company assumed that all people whose disease had not responded to treatment were hospitalised for an average of 26.6 inpatient days per year based on the resource-use estimates used in NICE’s psoriasis guideline. The company estimate of 26.6 days was based on 1 hospital admission in people with a high need (that is, those eligible for a first biological therapy) and 2.55 admissions in people with a very high need (that is, those eligible for a second biological therapy). The guideline was also used to source costs associated with best supportive care, which were estimated at approximately £888 per cycle in both populations modelled (DLQI more than 10 and DLQI 10 or less), based on an average of 26.6 inpatient days per year. The cost of apremilast was approximately £558 per cycle.

3.27 The company's model did not incorporate the cost of adverse events, or their impact on health-related quality of life (that is, reduced utility associated with each adverse event).

3.28 In the company's analysis of people with a DLQI score of more than 10, the sequence with apremilast dominated the sequence without apremilast. That is, the apremilast sequence was more effective (providing an additional 0.14 quality-adjusted life years [QALYs]) and less expensive (providing a cost saving of £3226). Adding data from the updated network meta-analysis (which, after consultation, included results from the PSOR-010 study) did not affect the cost-effectiveness results. In the company’s analysis of people with a DLQI score of 10 or less, the apremilast sequence (apremilast followed by best supportive care) dominated best supportive care alone (providing an additional 0.05 QALYs with a cost saving of £6300). In the company’s probabilistic sensitivity analysis, the apremilast sequence dominated the comparator sequence.

3.29 The company did scenario analyses to assess the uncertainty around structural assumptions. In addition, the company compared a sequence in which patients used apremilast after biological agents (adalimumab, then etanercept, then apremilast, then best supportive care) with the original sequence in which
apremilast came before biological therapies (apremilast, adalimumab, etanercept, best supportive care). In all scenario analyses, the apremilast sequence either dominated the comparator sequence without apremilast, or provided cost savings but with lower QALY gains. The sequence in which apremilast was positioned after the biological therapies was dominated by the original base-case sequence (apremilast before biological therapies).

3.30 The company also modelled apremilast as a replacement treatment for 1 of the biological therapies in the sequence. The apremilast sequences cost less, but were also less effective than the comparator sequences, with savings of £21,098–£39,121 per QALY lost.

ERG comments

3.31 For people with a DLQI score of 10 or less, the ERG considered best supportive care to be an appropriate comparator, but noted that the company did not present separate patient characteristics according to DLQI score.

3.32 The ERG noted that the company’s assumption that treatments had the same efficacy in all positions in the treatment sequence differed from NICE’s psoriasis guideline. The guideline found that efficacy of some biological therapies dropped when they were used second line (based on a meta-analysis of infliximab and ustekinumab).

3.33 The results of the company's network meta-analysis showed a placebo response for best supportive care (the mean absolute probabilities of a PASI 50, PASI 75 and PASI 90 response were 17%, 6% and 1% respectively). However, the company's model assumed best supportive care provided no benefit. The ERG noted that this was not consistent with the trial results or the approach used in NICE's psoriasis guideline. In the guideline model, about 4% of people receiving best supportive care had a PASI 50 response.

3.34 The ERG considered that it is uncertain if all treatments have the same withdrawal rates (20%) because of the different forms of administration, mechanisms of action and efficacy of all the treatments.

3.35 The ERG had several concerns with the company's utility values for people with a DLQI score of more than 10:
• the company did not use the EQ-5D data collected in clinical trials of apremilast

• the company did not appropriately justify the mapping algorithm used; there are other published algorithms with better predictive statistics and the company’s analysis may overestimate the benefit of apremilast

• the company used a mapping algorithm that was based on etanercept data, thereby assuming that apremilast and etanercept have the same effect on health-related quality of life for any given change in PASI score.

3.36 The ERG considered that it was appropriate to use PSOR-008 and PSOR-009 trial data for the analysis in people with a DLQI score of 10 or less, but suggested that data from PSOR-010 also should have been included. The ERG considered that assuming the same baseline utility value (0.7) regardless of DLQI score was not clinically plausible, and contradicted the assumptions of the EQ-5D mapping algorithm.

3.37 The ERG considered the cost associated with best supportive care to be the most important model input because the estimates of the incremental cost-effectiveness ratios (ICERs) were driven by the difference in costs and outcomes with apremilast compared with best supportive care. The ERG stated that, because of the company assumption that best supportive care costs more than apremilast (based on NICE’s psoriasis guideline), a sequence in which active therapy within a 10-year fixed timeframe is extended with apremilast (and consequently best supportive care is shortened) will always dominate the same sequence without apremilast.

3.38 The ERG had 3 concerns with using cost estimates for best supportive care from the psoriasis guideline:

• The definition and cost of best supportive care in the guideline was developed in the context of people with moderate to very severe plaque psoriasis who were being considered for a second biological therapy, and therefore may not be generalisable to the company's proposed positioning of apremilast in people with a DLQI score of more than 10 because these people are being considered for a first biological therapy.

• The definition of best supportive care in the guideline may be not generalisable to the company's model of people with a DLQI score of 10 or less because this group of patients is not eligible for biological therapies.
The Guideline Development Group for the guideline recognised that there were substantial uncertainties in its estimated resource use costs for best supportive care, and performed and considered extensive sensitivity analyses when making the guideline recommendations.

3.39 For other costs in the model, the ERG considered the company's application of costs for treatment acquisition and administration appropriate, but the ERG had concerns about the costs associated with monitoring, drug wastage and adverse events. The company assumed that people receiving apremilast needed 3 fewer physician visits per year than people receiving biological therapies. The ERG’s clinical adviser considered that the frequency of monitoring visits in clinical practice was likely to be similar regardless of treatment. The ERG noted that the frequency of monitoring had implications for treatment wastage; fewer physician visits could mean that more medication is prescribed at one time, which could result in more wasted medication when the person withdraws from treatment. The ERG considered that excluding costs of adverse events may favour apremilast, given that the company positioned apremilast as an additional line of treatment rather than replacing an existing one.

ERG exploratory analyses

3.40 The ERG conducted several exploratory analyses. The ERG’s preferred scenario included the combination of the following analyses:

- Addition of the company’s updated network meta-analysis (including data from PSOR–010) to the analysis in people with a DLQI score of more than 10.

- The ERG explored 4 scenarios that varied the costs associated with best supportive care. It stated that its preferred estimate was based on a publication by Fonia et al. (2010; adjusted for inflation to reflect 2012–13 prices), which assumed 0.312 hospital admissions of 20.8 days regardless of need. The ERG’s preferred estimate lowered the cost per cycle of best supportive care to about £348 per cycle.

- In the company’s base-case analysis, the company assumed that best supportive care provided no benefit. The ERG developed 4 alternative scenarios and stated that its preferred estimate was based on the base case in NICE’s psoriasis guideline (4% of people had a PASI 50 response with best supportive care).
For people with a DLQI score of more than 10, using EQ-5D data directly obtained from 3 apremilast trials (PSOR-008, PSOR-009 and PSOR-010) instead of a mapping algorithm.

3.41 The ERG's other exploratory analyses used the company's treatment sequences (that is, a sequence extended by apremilast compared with a sequence without apremilast) but varied the:

- probability of response to treatment (by including the company's updated network meta-analysis with PSOR-010 data)
- cost associated with best supportive care
- effectiveness of best supportive care
- approach to calculating health-related quality of life (by using trial-based EQ-5D data instead of a mapping algorithm)
- withdrawal rates associated with all treatments
- assumptions about treatment waste.

Following consultation, the company noted that it had made an error in its original submission when it used EQ 5D data based on US rather than UK tariffs. The company presented updated, corrected EQ 5D trial data for people with a DLQI score of more than 10. The ERG agreed that using UK tariffs was appropriate. For people with a DLQI score of more than 10, the apremilast before biological therapy sequence was associated with an incremental cost of £2611, incremental QALYs of 0.09 and an ICER of £28,574 per QALY gained, compared with a sequence without apremilast. The preferred analysis for people with a DLQI score of 10 or less did not include EQ 5D data from trials and was based on the US tariff. The ICER for the apremilast sequence was £89,374 per QALY gained, compared with a sequence without apremilast.

3.42 The ERG further varied rates of withdrawal associated with all treatments, and assumptions about how much is wasted when patients stop or change treatments. In its base case, the company applied a 20% annual withdrawal rate to all treatments. The ERG applied a higher annual withdrawal rate, based on results from the PSOR-008 trial of apremilast (marked as 'academic in confidence' by the company). The ERG did additional scenario analyses that showed that its cost-effectiveness results were sensitive to different costs associated with monitoring and waste. In the first scenario, the ERG assumed
that everyone would have the same number of physician visits (n=4) regardless of treatment. In an alternative scenario, the ERG assumed that patients who withdrew from apremilast would have 3 months of wasted medication (at a cost of £1787). The ERG also explored a scenario assuming 6 months of wasted medication at a cost of £3575. All 3 assumptions increased the ICER in both populations. The ERG suggested that 6 months of wasted medication might represent the average waste if people were prescribed medication only once a year.

3.43 Full details of all the evidence are available.

Additional analyses submitted by the company

3.44 During the consultation period, the company submitted a revised cost-effectiveness analysis for people with severe psoriasis (PASI score 10 or more, DLQI more than 10), comparing apremilast in a sequence before biological therapies with a sequence without apremilast. The company incorporated the following amendments suggested by the ERG and preferred by the Committee:

- using network meta-analysis results including the PSOR-010 trial
- and using trial-based EQ-5D data (using UK tariffs)
- and assuming that people receiving best supportive care would derive some clinical benefit
- and assuming that patients on different treatments have the same number of visits to the doctor (n=4).

3.45 The company also incorporated the ERG's preferred approach of basing estimates of resource use associated with best supportive care from Fonia et al. (2010), while at the same time maintaining that this study underestimated the rate of hospitalisation, and that defining best supportive care as in the NICE guideline on psoriasis was more appropriate. The company also presented hospital episode statistical data, which estimated that the average length of hospital stay for patients with a primary diagnosis of psoriasis was 3.5 days. Additionally, the company stated that the ERG's assumption was implausible that patients whose psoriasis does not respond to an active therapy will, when starting and trialling a new active treatment, incur the same resources as those
having best supportive care. The company stated therefore that it considered a
cost of £345 per cycle for disease that does not respond to be too high. The
company explored using costs from Fonia et al. (2010), reflecting the costs
incurred after biological therapy as a proxy for the period in which patients trial
new active treatments. However, in its preferred analysis, the company reduced
the costs associated with being admitted to a day ward for infliximab infusion,
and also reduced the costs associated with outpatient visits to avoid 'double
counting'. This resulted in the company estimating costs for people whose
disease has not responded and who are trialling new treatments of £45.04 per
28-day cycle. The company did not alter its pre-existing assumption of the
model that 20% of patients withdraw from biological therapies each year. The
company's revised base-case ICER comparing apremilast in a sequence before
biological therapies with a sequence without apremilast was £20,593 per QALY
gained (difference in QALYs 0.09, difference in costs £1882).

3.46 The company presented a scenario analysis that assumed that people whose
condition does not respond to drugs that have already been dispensed waste an
average of 14 days' worth of the drug at a cost of £275. This increased the
company's base-case ICER to £23,419 per QALY gained for apremilast in a
sequence before biological therapies compared with a sequence without
apremilast. Additionally, the company explored using different resource-use
costs for people whose condition does not respond, referred to as
'non-responders' (see table 3).

Table 3 Company exploratory analyses on non-responder costs (DLQI 10 or more):
cost-effectiveness results for an apremilast sequence compared with a sequence
without apremilast

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Non-responder cost estimate* (£)</th>
<th>Inc. cost (£)</th>
<th>Inc. QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company base case assuming resource use for non-responders in trial period for biological therapy, based on costs derived from the 12-month period after starting a biological therapy, from Fonia et al. (2010), less day-ward costs relating to infliximab infusion and less outpatient visits</td>
<td>£45.04</td>
<td>£1882</td>
<td>0.09</td>
<td>£20,539</td>
</tr>
</tbody>
</table>
Assuming resource use for non-responders in trial period for biological therapy, based on costs derived from the 12-month period after starting a biological therapy – from Fonia et al.

<table>
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<tr>
<th></th>
<th>£108.00</th>
<th>£2015</th>
<th>0.09</th>
<th>£23,035</th>
</tr>
</thead>
</table>

Assuming no resource use for non-responders in the trial period for biological therapy

<table>
<thead>
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<th>£0.00</th>
<th>£1724</th>
<th>0.09</th>
<th>£18,868</th>
</tr>
</thead>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; QALY, quality-adjusted life year.

3.47 The ERG agreed that an assumption of 2 weeks' waste for apremilast, and assuming equal number of physician visits between treatments (n=4), was appropriate. This increased the ERG's preferred ICER from £28,574 to £35,029 per QALY gained for apremilast in a sequence before biological therapies, compared with a sequence without apremilast. The ERG looked at the company's preferred approach to estimating costs associated with best supportive care needed when starting another active treatment in people whose psoriasis does not respond to a therapy; it acknowledged the importance of eliminating double counting and supported excluding outpatient and drug costs. However, the ERG disagreed with the company that costs derived from the 12-month period after starting a biological therapy were more appropriate because this would include both people whose disease did or did not respond to biological therapy and therefore would underestimate the costs involved. Instead, the ERG considered that costs based on the 12-months before a patient starts a biological therapy were more appropriate. This would result in costs of £225 per cycle for people whose disease did not respond, associated with an ICER of £30,311 per QALY gained for apremilast in a sequence before biological therapies, compared with a sequence without apremilast.
4 Consideration of the evidence

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

Clinical management

4.1 The Committee heard 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, face and genitals. Severe psoriasis is also associated with a shortened life expectancy. The Committee heard that, because psoriasis is visible to others, 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. It heard from clinical experts that people with severe psoriasis are about 6 times more likely to have suicidal thoughts or commit suicide than the general population. The Committee agreed that severe psoriasis has a significant psychosocial impact and substantially decreases quality of life.

4.2 The Committee discussed how clinicians assess the severity of disease in people with psoriasis. It understood that several indices are used, and heard that clinicians routinely use both the Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) to monitor the disease. The Committee was aware that the UK marketing authorisation for apremilast includes people with moderate and severe disease. It understood that, while the marketing authorisation did not specify the criteria for moderate or severe disease, the regulatory decision was based on trials that included people with a baseline PASI score of 12 or more (mean score 19), 10% or greater of body surface area affected, and a static Physician Global Assessment score of at least 3. The Committee noted that the trials did not stipulate that patients have a particular DLQI score at baseline. The Committee was aware that previous NICE technology appraisals defined severe psoriasis as a PASI score of 10 or more and a DLQI of more than 10. It understood that there is no universally accepted definition of moderate psoriasis. However, the Committee heard from clinical experts that, in practice, moderate disease would be characterised by a lower
PASI score (between 5 and 9). It noted that the company, in its submission, presented analyses in people with a PASI score of 10 or more and a DLQI score of 10 or less to represent people with disease not severe enough to be treated with biologicals in the UK. Clinical experts explained that the disadvantages of the DLQI are that it is not specific to psoriasis and does not capture all of the impacts of the disease (such as anxiety and depression). Clinical and patient experts suggested that some people with chronic psoriasis can develop coping mechanisms and so adjust to the impact of the disease, resulting in lower DLQI scores. The Committee heard that clinicians use the DLQI for treatment decisions with biologicals, but do not generally use it to define different levels of severity. The Committee acknowledged that PASI and DLQI, which reflect the outcomes used in the trials, are relevant measures used in clinical practice in the NHS. The Committee concluded that the evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice.

4.3 The Committee considered the treatment pathway for people with psoriasis. It was aware that people have topical treatments as first-line treatment, followed by conventional (non-biological) systemic therapies (such as methotrexate or ciclosporin), and phototherapy. If these treatments do not adequately control the psoriasis, people may have biological treatments, which they continue to have as long as the drugs work. The Committee understood that if the disease no longer responds to a biological treatment, people will be offered another biological treatment. This pattern is likely to be repeated over their lifetime; clinical experts noted that people with psoriasis will often try many alternative biological agents in a short timeframe. The Committee heard that, for people whose disease does not respond to multiple biological agents, the only remaining treatment option is best supportive care, which usually consists of topical agents and bandaging. The Committee questioned whether best supportive care was effective in treating psoriasis (that is, whether it improved PASI score or other measures of disease). It heard from clinical experts that best supportive care can be effective in the short term. The Committee was aware that best supportive care can be accompanied by disutility because of the intensive time-consuming, inconvenient and unpleasant treatments, and that the psoriasis may worsen sooner than with biological therapies. The Committee concluded that best supportive care is associated with limited, short-term efficacy and recognised the value of having a range of treatments with different mechanisms of action available.
4.4 The Committee considered the potential positioning of apremilast in the treatment pathway in clinical practice. It noted that the marketing authorisation for apremilast allows it to be positioned before, instead of, and after biological therapies. The Committee heard from a clinical expert that apremilast would generally be prescribed in people who had already tried biological therapies because apremilast is less effective than biological therapies. The clinicians also considered that patients unable to take biological therapies might be offered apremilast but that, in general, apremilast would not displace a biological therapy in the treatment pathway. The clinicians agreed that the positioning of apremilast (either before or after biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections. The Committee heard from the patient expert that because apremilast is less effective than biological therapies, offering apremilast as a first-line treatment could delay more effective treatments, and apremilast may therefore not be preferred. The Committee heard from clinical experts that some people with psoriasis do not adhere to treatment, so it is important to consider the patient’s choice of treatment to encourage adherence. It heard from the patient expert that apremilast is taken orally; some patients may prefer this but it could become a burden to some, given its twice-daily dosing and the life-long duration of psoriasis. By comparison, some biological therapies are administered only once every 3 months, by subcutaneous injection. One clinical expert noted that some people would avoid additional treatments if their psoriasis had already responded to therapy, even if the psoriasis had not been completely cleared. An advantage of apremilast over biological agents, noted by the clinical experts, is that apremilast is not contraindicated in people with tuberculosis. The Committee concluded that clinicians would like to prescribe apremilast, either before or after biological therapies, and that the decision would be driven partly by patient choice, and patients may well choose not to have apremilast before biological therapies because it is considered to be less effective.

Clinical effectiveness

4.5 The Committee considered the baseline characteristics of the patients in the apremilast trials and discussed whether the trials reflected the UK population with psoriasis who would be eligible to have apremilast. It noted the Evidence Review Group’s (ERG’s) comment that only 13% of the PSOR-008 trial population would be eligible for apremilast. The Committee heard from the
company that, in its view, the ERG had misinterpreted the intended positioning of apremilast. The company clarified that, according to the UK marketing authorisation, apremilast could be used after only 1 conventional systemic treatment, which could be phototherapy. The company stated that about 65% of the PSOR-008 and PSOR-009 trial populations had any prior systemic therapy (including conventional therapies but also biological agents). The Committee noted the ERG’s comments that the PSOR-008 and PSOR-009 trials may have overestimated the benefit of apremilast; some patients in the trial had no previous systemic treatment, so their disease would have been more likely to respond to apremilast because it was less severe than in people who had more treatments. The Committee heard from clinical experts that there is no robust evidence to suggest that previous treatment with conventional therapy affects response to subsequent treatment, but the Committee did not consider that this fully addressed the ERG’s concerns. The Committee heard from the company that other criteria for inclusion and exclusion used in apremilast trials were similar to trials of biological therapies. The Committee concluded that the apremilast trials broadly provided an appropriate basis for its decision making.

4.6 The Committee discussed the results of the apremilast clinical trials, and considered the company’s network meta-analysis, which compared apremilast with other biological agents specified in the scope. It noted that clinical trial evidence showed that apremilast was more effective than placebo for key outcomes at 16 weeks, and that this benefit was consistent across subgroups studied (see section 3.16). The Committee heard from clinical experts that biological therapies are more effective than apremilast for treating psoriasis, and was aware that the company’s network meta-analysis showed that the probability of response to treatment is highest with biological therapies and lowest with apremilast (see section 3.12). The Committee heard from the ERG that the company’s network meta-analysis was technically robust, but any bias from trials would carry through to the results from this analysis. The Committee heard that the ERG compared the meta-analysis results for the apremilast: etanercept comparison with odds ratios calculated using results of the PSOR-010 trial, confirming that psoriasis is more likely to respond to etanercept than apremilast. The Committee was aware of the drawbacks of the PSOR-010 study in that it was powered to compare apremilast with placebo and etanercept with placebo (but not apremilast with etanercept), but still concluded that apremilast is more effective than placebo, but not as effective as biological therapies.
The Committee discussed the long-term effectiveness of apremilast, noting that a substantial proportion of people who had a PASI 75 response after 16 weeks of apremilast treatment subsequently lost their PASI 75 response during the treatment withdrawal phase (marked as 'academic in confidence' by the company). The Committee heard from the company that some of the people in the apremilast trials who lost response, later regained it. The company stated that everyone who had a PASI 75 response at week 16 had at least a PASI 50 response by week 52. The clinical experts stated that fluctuating PASI scores characterise the natural history of psoriasis and any decline in efficacy with apremilast is expected to be similar to a decline with biological therapies. The experts also stated that the same level of response would not be seen if patients were to stop and restart treatment with apremilast. The Committee concluded that some response to treatment with apremilast is maintained up to 1 year, but noted uncertainty about longer-term effectiveness beyond the clinical trial data.

When considering the tolerability of apremilast, the Committee heard from clinical experts that apremilast is associated with a number of adverse events early in treatment. The Committee heard that the most common adverse events with apremilast are related to the gastrointestinal tract (including diarrhoea and nausea), and that people are willing to tolerate gastrointestinal adverse effects if they are benefiting from the drug. The Committee concluded that apremilast is associated with gastrointestinal adverse events, but these would not preclude the use of apremilast.

The Committee discussed the probability of people stopping apremilast treatment, and heard from clinical experts that the rate of withdrawal from apremilast is similar to (or potentially lower than) the rate of withdrawal from biological therapies. It heard from the company that the ERG's reference to a higher withdrawal rate with apremilast based on PSOR-008 data was factually inaccurate (the company marked this withdrawal rate as 'academic in confidence'). The company stated that 2-year data from PSOR-008 indicate a withdrawal rate of 19.5% per year for apremilast, which is similar to the company's assumption of a 20% withdrawal rate for biological therapies, which it chose based on the rate used for biological therapies in previous NICE appraisals (adalimumab, etanercept, infliximab, secukinumab and ustekinumab). The Committee concluded that the probability of people stopping treatment with apremilast is likely to be similar to the probability of people stopping treatment with biological therapies.
4.10 The Committee considered whether the company’s health economic model included relevant treatment sequences and positions. The Committee noted that the treatment sequences modelled by the company reflected the likely positioning of apremilast according to the clinical experts (see section 4.4), although this differed from NICE’s original scope for this appraisal. The Committee heard from clinical experts that etanercept is the least effective of the existing biological therapies for treating severe psoriasis. When queried, the company stated that it had selected etanercept for the model because it is the most used biological therapy for psoriasis in Europe. The ERG stated that this would not be a key driver of the results because the model includes biological therapies in both arms in the model and would not be displaced in the sequence including apremilast. Based on the likely positioning of apremilast in the treatment pathway (see section 4.4), the Committee concluded that, although the company did not compare the sequence in which apremilast came after biological therapies with a sequence without apremilast, the positions and comparisons modelled by the company were generally sufficient for decision making.

4.11 The Committee discussed the sources used by the company to estimate resource use and costs associated with best supportive care. It noted that the incremental cost-effectiveness ratios (ICERs) were highly sensitive to these inputs, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010; the ERG’s preferred assumption of best supportive care costs of £348 per cycle based on 6.49 days of hospitalisation per year) or NICE’s psoriasis guideline (the company’s base case assuming best supportive care costs £888 per cycle based on 26.6 days of hospitalisation per year). The Committee heard from the clinical experts that both sources were likely to overestimate the actual number of hospital days and resource use associated with best supportive care. This is in part because the populations described in Fonia et al. and NICE’s guideline differed from the population covered in this appraisal; NICE’s psoriasis guideline was for a specific, high-need subpopulation with very severe psoriasis, and Fonia et al. described care in a tertiary care centre known for treating the most severely affected people. The Committee heard from the company that the Fonia et al. study reflected a site that offered day care and therefore admitted fewer people to hospital than would normally be admitted in clinical practice. The clinical expert stated that the Fonia et al.
study describes a day unit that offered on-site hotel accommodation to people. The Committee noted that this option is much less costly than a hospital stay because it would not incur nursing and other hospital costs and, increasingly, is the model of care for people with psoriasis in the NHS. The Committee also heard from the clinical experts that, in recent years, the number of people hospitalised for severe psoriasis has fallen, and that clinicians give best supportive care to people during their outpatient visits; therefore, hospitalisation costs associated with psoriasis have fallen, and are continuing to fall. The Committee noted that after consultation, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with best supportive care was 3.5 days. It heard from the company that, in its view, these values underestimate actual length of NHS hospitalisation because they include people with different disease severities as well as people receiving concomitant medication and that, in patients who had received inpatient care, the average length of stay is 10.74 days. The clinical experts agreed that the hospital episode statistics data underestimated length of hospitalisation. The Committee agreed with this, but considered that the most plausible estimate would be lower than the ERG and company assumptions of 6.49 and 26.6 days per year. With respect to the proportion of people admitted to hospital, the clinical experts noted that the actual proportion is much lower than the 30% annual probability assumed by Fonia et al. (the lower of the 2 estimates). The Committee recognised the significant uncertainty in this model input, and agreed that the best supportive care costs are likely to be lower than in Fonia, and also noted that assuming a lower cost would increase the ICER. Additionally, the Committee noted that costs associated with hospitalisation were consistently applied to all days in hospital. The Committee, however, considered that it was reasonable to expect that the first few days in hospital would generate more expenses than later days; therefore the company may have overestimated the overall costs of best supportive care associated with hospitalisation in the model and accounting for this was likely to increase the ICERs presented. The Committee recognised the considerable uncertainty and concluded that shortcomings exist among all sources of data for resource use, but that resource use for best supportive care is closer to Fonia et al. than to the estimates from NICE’s guideline psoriasis.

4.12 The Committee went on to discuss the cost estimates for people whose disease does not respond to 1 systemic treatment and who then go on to get another, during which time they need elements of best supportive care. The Committee
recognised this as a significant driver of cost-effectiveness results. The Committee heard that the company had originally assumed that this resource would be lower than best supportive care costs and included an estimate of £460 per cycle, based on its preferred best supportive care costs from the NICE guideline on psoriasis (see section 4.11). The ERG instead based its preferred estimate on the study by Fonia et al. (2010) and also assumed that this additional resource is the same as for best supportive care, therefore including an estimate of £348 per cycle. After consultation, the company explored the effect on the cost-effectiveness results of using the costs from Fonia et al. for the 12-month period after patients start biological therapies. However the company noted that because it had already included costs for outpatients and systemic treatments in its model (also from Fonia et al.), it deducted these costs to avoid double counting, resulting in a cost for people whose condition does not respond of £45 per cycle. The Committee agreed that avoiding double counting was appropriate, but also agreed with the ERG that using costs from the period after starting biological therapies includes costs for people whose condition responds, as well as costs for people whose condition does not respond, to biological therapies, therefore underestimating the true costs. Instead, the Committee preferred the ERG’s inclusion of costs from Fonia et al. that reflect the 12-month period before a person starts a biological therapy while at the same time reducing the costs of outpatient and systemic treatments (£225 per cycle). The company agreed during the second Committee meeting that this estimate was plausible, but highlighted that the ERG applied this cost to all people starting a new biological therapy for the 16-week ‘trial’ period, whereas a proportion of people on new treatments benefit immediately or at least quickly. The company acknowledged that there was uncertainty around the proportion of patients to which this ‘non-responder’ cost should apply. The clinical experts agreed that response varies among people who try new active treatments, and that it is unlikely that all people will incur the same ‘non-responder’ costs. The Committee heard from the ERG that the costs from Fonia et al. include patients at different levels of response and therefore the model already accounted for variable ‘non-responder’ costs during the period in which modelled patients try new drugs. The Committee concluded that there was considerable uncertainty about the actual costs associated with starting a new therapy if a person’s disease has previously not responded to another therapy in the model, but concluded that the ERG’s estimate of £225 per cycle was the most plausible of those presented.
4.13 The Committee considered the quality-of-life and utility values used in the company's original model. It was aware that the company did not use the baseline EQ-5D data collected in the apremilast clinical trials. The Committee heard that the company sourced the baseline utility value in the model (0.7) from previous technology appraisals (adalimumab, etanercept, infliximab, secukinumab and ustekinumab), and noted that people in the apremilast clinical trials had a baseline utility value of 0.8. The company stated that the baseline EQ-5D value in the apremilast trials differed from the baseline value in trials of biological therapies (although other key baseline characteristics such as PASI score were consistent across the trials). The ERG confirmed that changing the baseline utility value used in the model would not significantly affect the cost-effectiveness results because the model is driven by the incremental changes in utility score from baseline. The Committee then discussed the company's approach to incorporating utility increments associated with a response to treatment in the model. The Committee was concerned that the company had included trial-based EQ-5D data in its model reflecting a DLQI score of 10 or less but that, in the model reflecting a DLQI score of more than 10, the company had used a mapping algorithm instead of clinical trial data. The company was also concerned that the company used etanercept data in the mapping algorithm instead of apremilast data. The company justified this on the basis that EQ-5D data in the apremilast trials were subject to a ceiling effect. However, following the first Committee meeting the company clarified that it had, in error, derived EQ-5D data from US instead of UK tariffs. The company agreed that the updated trial-based EQ-5D data were appropriate and presented revised results for the change in utility from baseline associated with the different PASI response categories in the model. The Committee noted that the company's models did not take into account the disutility values associated with adverse events, but the ERG was unable to comment on how including these values would have affected the ICER. The Committee concluded that the utility gains estimated from the company's revised model (for people with a DLQI score of more than 10) were plausible.

4.14 The Committee discussed the assumption in the company model that apremilast is associated with fewer visits to a physician than biological therapies (1 annual visit for apremilast, compared with 4 visits per year with biological therapies). The Committee heard from the clinical experts that because apremilast is a new drug dermatologists would be cautious in allowing fewer visits to a physician, and therefore the number of physician visits (including GP visits in 'shared care'
arrangements) for apremilast and biological therapies would be the same initially but, in the long term, the clinicians expected that the number of monitoring visits would be lower for apremilast. The Committee did not consider it realistic that people receiving apremilast would visit their physician only once each year, and concluded that 4 visits per year (including visits to GPs) is more appropriate (based on the company's assumption of 4 visits for biological therapies). The clinical experts agreed with this, but noted that monitoring costs for apremilast were likely to be lower than for biological therapies. The clinical experts also confirmed that for treatment with apremilast GPs could monitor patients under shared-care arrangements. However, the Committee noted that the cost of monitoring people on apremilast in primary care should reflect the assumption of additional payments to GPs, similar to arrangements for monitoring methotrexate. The Committee noted that if lower monitoring costs for apremilast were incorporated in the model, this would lower the ICERs presented, but acknowledged the lack of robust estimates available. Therefore, the Committee concluded that the assumption of equal monitoring visits was appropriate. The Committee discussed the potential for waste with apremilast. The clinical experts acknowledged that when people did not adhere to or withdrew from treatment, some tablets would be wasted. The Committee considered that it would be reasonable to account for some treatment waste with apremilast. It noted the company's revised model, which included an assumption of 14 days' wasted treatment; it heard from the ERG and experts that this was plausible. The company additionally stated that a waste assumption should be applied equally to biological therapies and apremilast. The ERG, however, considered that the waste for biological therapies in each arm of the model would cancel each other out but the company stated that would be true only if a lifetime horizon was assumed. The clinical experts also stated that while there will be waste with biological therapies, this is low because people get rigorous training before being prescribed biological therapies, in order to boost adherence. The Committee concluded that the assumption of 14 days' apremilast waste in the revised model was appropriate.

4.15 The Committee discussed the company's assumption that the probability of response for each treatment was the same regardless of its position in the sequence. It heard from the company that clinical trials show that the efficacy of apremilast appears consistent across the positions in the treatment sequence. The company noted that the response was slightly lower if apremilast were
positioned after biologicals, and that its model accounted for this reduced efficacy. The Committee was satisfied that the company had included the efficacy of apremilast appropriately in its model.

4.16 The Committee considered the other assumptions in the company model in light of its clinical discussion. It concluded that the model should include the possibility that psoriasis can improve with best supportive care (in contrast to the company’s assumption of no effectiveness, see section 4.3). The Committee agreed with the company’s assumptions that withdrawal rates are similar for apremilast and biologicals (see section 4.9), and that response rates remain relatively constant over time (see section 4.7).

4.17 The Committee discussed the ICERs for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of more than 10. The Committee considered the company’s revised base-case results and the ERG’s exploratory analyses. The Committee concluded that the most plausible ICER available for decision-making was about £30,300 per QALY gained and noted that this was above the range normally considered cost effective. However it noted that there was considerable uncertainty about key factors driving this ICER, such as monitoring costs (see section 4.13), amount of drug waste (see section 4.14), the likely costs associated with best supportive care (see section 4.11) and the costs associated with ‘non-responders’ (see section 4.12). The Committee considered that these uncertainties could drive the ICERs in different directions and the magnitude of impact was uncertain. However, the Committee recalled its consideration in section 4.11 that the costs associated with best supportive care are likely to be even lower than those estimated by the ERG from Fonia et al. (2010) and accounting for this would increase the ICER. Moreover, being mindful that apremilast was not as effective as biological therapies, the Committee noted comments from the consultation and from the patient expert that apremilast in a sequence before biological therapies could delay access to more effective treatment, and may therefore not be preferred. The Committee heard from the patient expert that achieving clear skin in the shortest possible time is important to people and that a PASI 75 response shown with apremilast means that people are still affected by psoriasis. Together with the uncertainties in the economic modelling, the Committee concluded that apremilast could not be recommended for severe psoriasis after the failure of conventional systemic therapy but before biological therapy.
4.18 The Committee discussed the ICERs for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of 10 or less (moderate disease), and where best supportive care was the only comparator because patients with moderate disease are not offered biological therapies. At its first meeting, the Committee concluded that the most plausible ICER for the apremilast sequence lay somewhere between £97,500 and £125,300 per QALY gained, taking into account its preferred assumptions. The Committee noted that the company had not updated this analysis with the UK tariff-based utility values, and estimated, based on the original modelling, that the ICER in the less severely affected population could be twice that seen for the population with a PASI and DLQI of 10 or more, that is, about £60,000 per QALY gained. The Committee noted that the evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice (a PASI score of 5 to 9). Given that the company's model indicated that apremilast had a higher ICER in a less affected population (that is, people with a DLQI score of 10 or less), the Committee concluded that the ICER for apremilast for treating moderate psoriasis would not be within the range considered to be a cost-effective use of NHS resources.

4.19 The Committee considered the company's cost-effectiveness results for apremilast positioned after biological therapies and before best supportive care. It noted that the sequence in which apremilast was positioned after biological therapy was dominated (provided fewer QALYs at a higher cost) by the sequence in which apremilast came before biological agents. Having already concluded that apremilast, as a treatment in a sequence before biological therapy, is not a cost-effective use of NHS resources (section 4.17), the Committee concluded that a treatment sequence that provides fewer QALYs but costs more could not be considered a cost-effective use of NHS resources.

4.20 The Committee considered the company's cost-effectiveness results for apremilast as a replacement treatment for 1 of the biological therapies in the sequence, even though the clinical experts stated that apremilast was unlikely to displace a biological agent in the treatment pathway. It noted that the sequences containing apremilast were cost saving – but less effective – than the comparator sequences, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £21,100 to £39,100 per QALY). The Committee considered that the ICERs were based on uncertain assumptions and noted that that ICERs based on its preferred assumptions were not available. The Committee noted
that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee concluded that the ICERs for apremilast as a replacement for biological therapies for severe psoriasis were not within the range considered to be a cost-effective use of NHS resources.

4.21 The Committee heard differing views about whether apremilast was innovative in its potential to make a significant and substantial impact on health-related benefits. It agreed that apremilast appeared to be innovative in its novel use of an existing mechanism of action, and agreed that it demonstrated innovation by providing an additional novel oral therapy. However, the Committee recalled that some people with psoriasis prefer less-frequent injectable treatments to more-frequent oral ones (see section 4.4) and therefore the Committee concluded that, in this respect, there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4.22 The Appraisal Committee considered when appraising apremilast whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. 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 not an applicable 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 on the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of cost effectiveness of apremilast.

4.23 The Committee discussed whether the recommendations could be considered unfair because a small group of people are unable to take any biological therapies because of contraindications that could be associated with protected characteristics according to the Equality Act. The Committee concluded that these patients would otherwise have best supportive care, and although the company did not present a revised ICER comparing apremilast with best supportive care for this group, the Committee expected the ICER to be around £60,000 per QALY gained. Considering that this was much higher than what is
normally accepted as good use of NHS resources, the Committee concluded that to recommend apremilast for this group would not achieve the legitimate aim of providing advice on cost-effective treatments.

**Summary of Appraisal Committee’s key conclusions**

<table>
<thead>
<tr>
<th>TA368</th>
<th>Appraisal title: Apremilast for treating moderate to severe plaque psoriasis</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key conclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apremilast is not recommended within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated.</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>The Committee concluded that the incremental cost-effectiveness ratios (ICERs) for apremilast for moderate and severe psoriasis were not within the range considered to be a cost-effective use of NHS resources.</td>
<td>4.17, 4.18, 4.19, 4.20</td>
<td></td>
</tr>
</tbody>
</table>

| **Current practice** | |
| Clinical need of patients, including the availability of alternative treatments | Severe psoriasis has a significant psychosocial impact and substantially decreases quality of life. People with psoriasis have topical treatments as first-line treatment, followed by conventional (non-biological) systemic therapies and phototherapy. If these treatments do not adequately control the psoriasis, people may have biological treatments. People with psoriasis will often try many alternative biological agents in a short timeframe and, for people whose disease has failed to respond to multiple biological agents, the only remaining treatment option is best supportive care. Although best supportive care can provide limited, short-term benefits, it is associated with disutility because of the intensive time-consuming, inconvenient and unpleasant treatments. | 4.1, 4.3 |

The technology
### Proposed benefits of the technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

Apremilast provides a novel use of an existing mechanism of action, and an oral alternative to injectable biological therapies. However, some people with psoriasis prefer less frequent injectable treatments to more frequent oral ones. Another advantage of apremilast over biological agents is that apremilast is not contraindicated in people with tuberculosis.

### What is the position of the treatment in the pathway of care for the condition?

The marketing authorisation for apremilast allows it to be positioned before, instead of, and after biological therapies. However, clinical experts did not consider that apremilast would displace a biological therapy in the treatment pathway, and agreed that the positioning of apremilast (either before or after biological therapy) would be largely driven by patient choice and intolerance or contraindications to biological therapy.

### Adverse reactions

The most common adverse events with apremilast are related to the gastrointestinal tract (including diarrhoea and nausea), but these would not preclude the use of apremilast because people are willing to tolerate gastrointestinal adverse effects if they are benefiting from the drug.

### Evidence for clinical effectiveness

<table>
<thead>
<tr>
<th>Availability, nature and quality of evidence</th>
<th>The clinical evidence for apremilast came from 4 multicentre, placebo-controlled, double-blind randomised controlled trials in people with moderate to severe chronic plaque psoriasis. The trials were good quality and the treatment groups were generally similar at baseline. Because PSOR-010 was not powered to compare apremilast with etanercept, and there were no other head-to-head trials comparing apremilast with any of the biological therapies currently recommended by NICE for psoriasis, the company did a network meta-analysis that included 24 studies. The Evidence Review Group (ERG) stated that the results from the company’s network meta-analysis were likely to be reasonably reliable, but that the results of the company’s sensitivity analysis should be interpreted with caution.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>Not everyone in the PSOR-008 and PSOR-009 trials had systemic therapies before starting the trial (a criterion of the UK marketing authorisation for apremilast). The ERG suggested that the PSOR-008 and PSOR-009 trials might have overestimated the benefit of apremilast because some patients in the trial had no previous systemic treatment, so their disease would have been more likely to respond to apremilast because it was less severe than in people who had more treatments.</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>The evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice (Psoriasis Area Severity Index [PASI] score between 5 and 9). The Committee were uncertain about the longer-term effectiveness of apremilast, beyond the clinical trial data (beyond 1 year).</td>
</tr>
<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The Committee concluded that apremilast is more effective than placebo but not as effective as biological therapies.</td>
</tr>
</tbody>
</table>
### Availability and nature of evidence

The company’s base-case model included a treatment sequence positioning apremilast before biological therapies (adalimumab and etanercept) and best supportive care compared with a treatment sequence without apremilast. The company provided scenario analyses assessing the cost effectiveness of apremilast positioned after biological agents (compared with a sequence with apremilast positioned before biological therapies) and apremilast as a replacement treatment for 1 of the biological therapies in the sequence. Given that clinical experts suggested that apremilast would extend the treatment sequence (either before or after biologicals), the Committee concluded that, although the positions and comparisons modelled by the company differed from NICE’s original scope for this appraisal, they were generally sufficient for decision-making.

### Uncertainties around and plausibility of assumptions and inputs in the economic model

The Committee considered that the company’s base-case results were based on uncertain assumptions about key factors driving this ICER, such as monitoring costs, amount of drug waste, the likely costs associated with best supportive care and the costs associated with 'non-responders'. The ERG addressed these uncertainties in its exploratory analyses.

### Incorporation of health-related quality-of-life benefits and utility values

<table>
<thead>
<tr>
<th>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?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following the first Committee meeting the company clarified that it had, in error, derived EQ-5D data from US instead of UK tariffs. The company agreed that the updated trial-based EQ-5D data were appropriate and presented revised results for the change in utility from baseline associated with the different PASI response categories in the model. The Committee noted that the company’s models did not take into account the disutility values associated with adverse events, but the ERG was unable to comment on whether including these values would have affected the model results. The Committee concluded that the utility gains estimated from the company’s revised model (for people with a Dermatology Life Quality Index (DLQI) score of more than 10) were plausible. There were no additional gains in health-related quality of life over those already included in the quality-adjusted life year (QALY) calculations.</td>
</tr>
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<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>Not applicable.</td>
<td></td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The ICERs were highly sensitive to the costs associated with best supportive care, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010) or NICE's psoriasis guideline. The Committee concluded that resource use for best supportive care is closer to Fonia et al. than to estimates from NICE's guideline.</td>
<td>4.11</td>
</tr>
<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>The Committee considered that the most plausible ICER available for the apremilast sequence (in which apremilast was positioned before biological therapies) was about £30,300 per QALY gained. However it noted that there was considerable uncertainty about key factors driving this ICER, such as monitoring costs, amount of drug waste, the likely costs associated with best supportive care and the costs associated with 'non-responders'. The Committee estimated that the ICER in the less severely affected population could be twice that seen for the population with a PASI and DLQI of 10 or more, that is, about £60,000 per QALY gained for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of 10 or less (moderate disease), and where best supportive care was the only comparator. The Committee concluded that a sequence in which apremilast is positioned after biological therapies would not be a cost-effective use of NHS resources because it is dominated by a sequence that was not considered cost effective (apremilast positioned before biological agents).</td>
<td>4.17, 4.18, 4.19</td>
</tr>
</tbody>
</table>
The Committee noted that the sequences in which apremilast replaced 1 of the biological therapies were cost saving but less effective than the comparator sequences, resulting in ICERs that reflected ‘savings per QALY lost’ (ranging from £21,100 to £39,100 per QALY).

<table>
<thead>
<tr>
<th>Additional factors taken into account</th>
<th>4.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient access schemes (PPRS)</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>End-of-life considerations</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>
5 Review of guidance

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

Andrew Dillon
Chief Executive
November 2015
6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

Mr Matthew Campbell-Hill
Lay member
Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Daniel Hochhauser
Consultant in Medical Oncology, UCL Cancer Institute

Mrs Anne Joshua
NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Sanjay Kinra
Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy
Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne
Professorial Fellow in Public Health, Wessex Institute, University of Southampton

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
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

Dr Nerys Woolacott
Senior Research Fellow, Centre for Health Economics, University of York
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.

Sophie Laurenson and Helen Tucker
Technical Leads

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager
7 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by CRD and CHE Technology Assessment Group (Centre for Reviews and Dissemination and Centre for Health Economics), University of York:


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, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Celgene

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):
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 apremilast by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Professor Anthony Bewley, nominated by Celgene – clinical expert
- Professor Catherine Smith, nominated by British Association of Dermatologists – 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.

- Celgene
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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