NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Apremilast for treating moderate to severe plaque psoriasis

1 Recommendations

1.1 Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and ultraviolet-A light), or when these treatments are contraindicated or not tolerated, only if:

- the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
- treatment is stopped if the psoriasis has not responded adequately at 16 weeks; an adequate response is defined as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from start of treatment
- the company provides apremilast with the discount agreed in the patient access scheme.

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

1.3 This guidance is not intended to affect the position of patients whose treatment with apremilast was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	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).
Marketing authorisation	'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)'.
Recommended dose and schedule	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).
Price	The price of apremilast is £550.00 for a 28-day pack (56×30 mg tablets) (excluding VAT; British National Formulary online, accessed July 2016). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of apremilast, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Celgene and a review of this submission by the evidence review group. This appraisal was a rapid review of the published NICE technology

appraisal guidance on apremilast for treating moderate to severe plaque psoriasis. It focused on cost-effectiveness analyses that included a patient access scheme agreement, which provides apremilast at a reduced cost. The discount is commercial in confidence. See the committee papers for full details of the rapid review evidence, and the history for full details of the evidence used for NICE's original technology appraisal guidance on apremilast for treating moderate to severe plaque psoriasis. See section 4.24 onwards for the rapid review consideration.

4 Committee discussion

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), a 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 participants 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 reflected people with severe 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 therapies, which they continue to have as long as the drugs work. The committee understood that if the disease no longer responds to a biological therapy, people will be offered another biological therapy. 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 NHS clinical practice. It noted that the marketing authorisation for apremilast allows it to be positioned:

- earlier in the treatment pathway than biological therapies (that is, after 1, but not all, other systemic therapies have failed; see section 4.5)
- after biological therapies (see section 4.6)
- instead of biological therapies (at the point when all other systemic therapies have failed; see section 4.7).

4.5 The committee considered whether apremilast would be used before biological therapies were considered, that is, after 1 but not all other systemic treatments had failed. It noted that the company had not presented analyses for apremilast in this position, and that it did not hear from clinical experts that they would offer the drug at this point. The committee therefore did not consider this position further.

4.6 The committee discussed whether apremilast would be used if biological therapies were not tolerated or after all biological therapies had failed. It heard from a clinical expert that apremilast would generally be prescribed for people who had already tried biological therapies, or for those who are unable to take them. The committee understood from the clinical experts that, in general, apremilast would not displace a biological therapy in the treatment pathway. It concluded that the most likely position for apremilast in the treatment pathway was if biological therapies were not tolerated or after all biological therapies had failed.

4.7 The committee discussed whether apremilast would be used at the same point in the treatment pathway as biological therapies (that is, once all other systemic therapies had failed). It heard from clinical experts that the positioning of apremilast (either before, or instead of, a 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, so patients may prefer biological therapies
- clinical experts that some people with psoriasis do not adhere to treatment, so it is important to consider patient choice to encourage adherence.
- the patient expert that apremilast is taken orally, which some patients may prefer but others may find a burden, given its twice-daily dosing (by comparison, some biological therapies are administered only once every 3 months, by subcutaneous injection)
- the clinical experts that an advantage of apremilast over biological agents is that it is not contraindicated in people with tuberculosis.

The committee agreed that apremilast may not be the preferred treatment at the point in the treatment pathway at which biological therapies are considered (that is, after all systemic treatment have failed), but clinicians would like to have the option to prescribe apremilast at this point. The committee recognised that the treatment decision would be driven by patient choice, and that patients may well choose not to have apremilast instead of biological therapies because it is considered to be less effective (see sections 4.8 to 4.12).

Clinical effectiveness

4.8 The committee appreciated that 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, -008, -009 and -010. The primary endpoint was the same in all 4 trials: a 75% reduction in the PASI score at week 16 (known as a PASI 75 response). The randomised period of all trials was only until week 16. 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 (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. 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 provided an appropriate basis for its decision-making.

4.9 The committee discussed the results of the placebo-controlled apremilast clinical trials, and considered the company's network meta-analysis, which indirectly 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. 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.

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.

4.10 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.

4.11 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.

4.12 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.

Cost effectiveness

4.13 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 to 4.7). 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 to 4.7), 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.

4.14 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 was 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 on psoriasis.

4.15 The committee went on to discuss the cost estimates for people whose disease does not respond to one systemic treatment and who then go on to get another one, 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 their 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.

4.16 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, 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 committee 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 was 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.

4.17 The committee discussed the assumption in the company model that apremilast is associated with fewer visits to a clinician 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 clinician and therefore the number of clinician visits (including GP visits in 'shared care' arrangements) for apremilast and biological therapies would be the same initially, but, in the long term, the clinical experts 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 clinician 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.

4.18 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.

4.19 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).

4.20 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 quality-adjusted life year (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 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.

4.21 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

4.22 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.

4.23 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.

4.24 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.

4.25 The 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 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 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.

4.26 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.

Rapid review

Population

4.27 The committee noted that the company's revised analyses focussed on people with severe disease, but the marketing authorisation also included people with moderate disease. The committee recalled its discussions with clinical experts that the evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice. The

committee concluded that there was no evidence for clinical or cost effectiveness available to enable it to make a decision for people with moderate disease.

Key assumptions

4.28 The committee noted that the company included the preferred assumptions in NICE's original appraisal of apremilast in the revised economic modelling (see Table 1).

Table 1 Company's preferred assumptions

Parameter	Committee's preferred inputs	Discussion reference
Cost of best supportive care per 28-day cycle	£348.22	Section 4.14
Cost of non-response	£225.00	Section 4.15
Source of utility estimates	Apremilast trial data	Section 4.16
Efficacy of best supportive care	National Clinical Guideline Centre model	Section 4.3
Efficacy of active treatments	Network meta-analysis including PSOR-010 study	Section 4.9
Wastage of apremilast	2 weeks	Not applicable
Clinician visits	Same number of visits for all active treatments	Section 4.17
EQ-5D value set	UK value set	Not applicable

The ERG confirmed that the company did this appropriately, and the committee agreed that the company had presented results based on the committee's preferred inputs.

Stopping rule

4.29 The committee considered a stopping rule for apremilast. It heard during consultation of the rapid review appraisal document that NICE guidance for the biological therapies in psoriasis includes a stopping rule. The committee recognised that the summary of product characteristics states that 'if a patient shows no evidence of therapeutic benefit after 24 weeks,

treatment should be reconsidered'. The committee understood, however, that the analyses it considered had included a stopping rule at 16 weeks. The committee recognised that NICE guidance for biological therapies for psoriasis defined 'no evidence of therapeutic benefit'; the committee did not hear anything during consultation or from the company during the appraisal of apremilast to change the criteria. The committee concluded that it was appropriate to include a stopping rule, and that this should be at 16 weeks and be defined in the same way as in NICE guidance for biological therapies in psoriasis.

Treatment sequences

4.30 The committee was aware that apremilast would be used in clinical practice after all systemic therapies had failed, but could be used before, after or instead of biological therapies (see sections 4.4 to 4.7). The company's base case compared a sequence of apremilast positioned before biological therapies against a sequence without apremilast. The company's scenario analysis compared a sequence of apremilast positioned before biological therapies against a sequence of apremilast after biological therapies. The ERG stated that the company had not explored a full range of sequences, so the optimal position of apremilast in the treatment pathway could not be established. The company clarified that it did not intend to position apremilast as an option only before biological therapies. The ERG also identified problems with external validity of treatment sequences that included biological therapies. The ERG found that, when comparing each biological therapy with best supportive care, the ICERs generated were more than £30,000 per QALY gained. The committee noted that the results were unexpected because these biological therapies have been previously recommended by NICE as a cost-effective use of NHS resources. The committee understood that this difference was driven by the incorporation of the committee's preferred assumptions, particularly around the costs of best supportive care. It was outside the committee's current remit to appraise the cost

effectiveness of biological therapies, so it did not explore this further. The committee agreed with the ERG that any treatment sequence including a biological therapy resulted in a lower ICER for the sequence that included apremilast compared with the sequence that did not include apremilast because apremilast up-front delayed giving biological therapies found to be cost ineffective in these analyses. The committee therefore agreed that it could not make a decision using ICERs based on these comparisons.

4.31 The company also presented results for sequences without biological therapies, defined as apremilast followed by best supportive care compared with best supportive care alone. The ERG considered this to be the only valid ICER available because the sequences did not include biological therapies (see section 4.26). The company's base-case ICER for apremilast followed by best supportive care was less than £30,000 per QALY gained compared with best supportive care alone (the precise ICER is commercial in confidence). The committee agreed that apremilast is a cost-effective use of NHS resources for people for whom best supportive care is the only option, that is, if biological therapies are not tolerated or after all biological therapies have failed.

4.32 The committee considered whether it could use the analyses of best supportive care to appraise apremilast for people with severe psoriasis for whom treatment with biological therapies was an option. The committee noted that apremilast was not as effective as biological therapies, and it was less costly. The committee agreed that it would have valued a direct comparison with biological therapies to understand the cost saved for each QALY lost, but recognised it had not been presented with this. The committee reiterated that the positioning of apremilast (either before or instead of biological therapy) would be driven largely by patient choice. The committee was aware that the results were comparable with the ICERs for biological therapies compared with best supportive care in previous NICE technology appraisals. The committee noted that patients value having a range of treatment options. It concluded that, because the

ICER for apremilast was comparable to those estimated previously for biological therapies, it could recommend apremilast as an option for treating severe chronic plaque psoriasis that has not responded to all systemic therapies, or when systemic therapy is contraindicated or not tolerated. This recommendation applies only when the company provides apremilast with the discount agreed in the patient access scheme.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Apremilast for treating moderate to severe plaque psoriasis	Section
Key conclusion		
4.33	Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and ultraviolet-A light), or when these treatments are contraindicated or not tolerated, only if: • the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 • treatment is stopped if the psoriasis has not responded adequately at 16 weeks; an adequate response is defined as: – a 75% reduction in the PASI score (PASI 75) from when treatment started or – a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from start of treatment • the company provides apremilast with the discount agreed in the patient access scheme.	**Error! Reference source not found.** 4.27

Apremilast was cost effective when compared with best supportive care. Apremilast was less effective but also less costly than biological therapies. The cost-effectiveness analyses, which compared apremilast with biological therapies, included treatment sequences. These were not considered appropriate for decision-making because the biological therapies in the sequence were not in themselves cost effective, which biased the results. However, the incremental cost-effectiveness ratio (ICER) for apremilast compared with best supportive care was comparable to ICERs for biological therapies in previous NICE technology appraisals. The committee recognised that treatment choice will be largely driven by patient preference, and agreed apremilast was a cost-effective use of NHS resources. There was no clinical- or cost-effectiveness evidence available to make a decision for people with moderate disease.		4.31 4.32
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 therapies. People with psoriasis will often try many alternative biological agents in a short timeframe and, for people whose disease has not responded to multiple biological agents, the only remaining treatment option is best	**Error! Reference source not found.**, **Error! Reference source not found.**

	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.	
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.	**Error! Reference source not found.**, **Error! Reference source not found.**
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.	**Error! Reference source not found.**

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.	**Error! Reference source not found.**
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	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 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.	**Error! Reference source not found.**
Relevance to general clinical	Not everyone in the PSOR-008 and PSOR-009 trials had systemic therapies before starting the trial (a criterion of the UK	**Error! Reference**

practice in the NHS	marketing authorisation for apremilast). The ERG suggested that PSOR-008 and PSOR-009 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.	**source not found.**
Uncertainties generated by the evidence	The evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice (total PASI score between 5 and 9). The committee was uncertain about the longer-term effectiveness of apremilast, beyond the clinical trial data (beyond 1 year).	**Error! Reference source not found.** **Error! Reference source not found.**
Are there any clinically relevant subgroups for which there is evidence of	Not applicable	

differential effectiveness?		
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that apremilast is more effective than placebo but not as effective as biological therapies.	**Error! Reference source not found.**
Evidence for cost effectiveness		
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 therapies (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 biological therapies), 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.	**Error! Reference source not found.**, **Error! Reference source not found.**

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 the ICER, such as monitoring costs, amount of drug waste, the likely costs associated with best supportive care and the costs associated with non-response. The ERG addressed these uncertainties in their exploratory analyses.	**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**
Incorporation of	Following the first committee meeting the	**Error!**

health-related quality-of-life benefits and utility values 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?	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 was 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 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.	**Reference source not found.** **Error! Reference source not found.**
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable	
What are the key drivers of cost effectiveness?	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	**Error! Reference source**

	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.	**not found.**
Most likely cost-effectiveness estimate (given as an ICER)	The committee considered that the most plausible ICER available for the apremilast treatment 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-response. The committee estimated that the ICER in the less severely affected population could be twice that for the population with severe disease; 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 treatment 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	**Error! Reference source not found.**, **Error! Reference source not found.**

	positioned before biological therapies). 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–£39,100 per QALY).	**Error! Reference source not found.** **Error! Reference source not found.**
Rapid review reconsideration	The rapid review only considered severe disease. The committee agreed it could not use ICERs based on comparisons of treatment sequences for decision-making. This was because biological therapies were not cost effective in these analyses, biasing the results. With the patient access scheme included, the	4.27 4.30

	ICER for apremilast compared with best supportive care was under £30,000 per QALY gained (the precise ICER is commercial in confidence). The committee agreed that apremilast was cost effective after biological therapies had failed, when best supportive care is the only treatment option. The committee recognised that apremilast was less effective than biological therapies, but that patient preference (mainly relating to method of administration) would influence whether it would be an appropriate treatment option. It noted that the ICERs compared with best supportive care were comparable to the ICERs for the biological therapies in the respective technology appraisals. The committee agreed that, for people for whom systemic therapies had failed and biological therapies were a treatment option, apremilast was a cost-effective use of NHS resources	4.31 4.32
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of apremilast. The level of the discount is commercial in confidence.	
End-of-life considerations	Not applicable	
Equalities	When using the DLQI, healthcare professionals should	

considerations and social value judgements	take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated and the doctor responsible for their care thinks that apremilast is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Celgene have agreed that apremilast will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details

of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

6 Review of guidance

6.1 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.

Amanda Adler
Chair, appraisal committee
July 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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.

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), and/or a technical adviser and a project manager.

Raisa Sidhu

Technical Adviser

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Project Manager

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