

Brodalumab for treating moderate to severe plaque psoriasis

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

- 1.1 Brodalumab is recommended as an option for treating plaque psoriasis in adults, only if:
- the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
 - the disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated and
 - the company provides the drug with the discount agreed in the patient access scheme.
- 1.2 Stop brodalumab at 12 weeks if the psoriasis has not responded adequately, 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 when treatment started.
- 1.3 When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.
- 1.4 When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.
- 1.5 These recommendations are not intended to affect treatment with brodalumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trial results show that brodalumab improves severe psoriasis more than placebo and

ustekinumab. When compared indirectly, it appears to be as effective as other anti-interleukin-17 agents. Cost-effectiveness estimates for brodalumab compared with other biological treatments, and with apremilast and dimethyl fumarate, show that it is generally more cost effective (that is, depending on the comparator, it costs less but is more effective, or costs more but is considerably more effective). Brodalumab can be offered as an option to people with severe psoriasis that has not responded to other systemic non-biological therapies.

2 Information about brodalumab

Marketing authorisation	Brodalumab (Kyntheum, Leo Pharma) is indicated for the treatment of 'moderate to severe plaque psoriasis in adults who are candidates for systemic therapy'.
Dosage in the marketing authorisation	The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks.
Price	<p>£1,280 per pack of 2 syringes of 210 mg/1.5 ml solution (excluding VAT; British national formulary [BNF] online [accessed January 2018]).</p> <p>The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of brodalumab, 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.</p>

3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Leo Pharma and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Experience of people with psoriasis

Psoriasis affects all aspects of a person's life

- 3.1 The committee understood that psoriasis at any level of severity can be distressing and debilitating, affecting all aspects of life (physical, psychological, social and financial). It noted that having treatments which are associated with few or manageable side effects, and which are effective on the face, hands, feet and genitals, is important to people with psoriasis, as is having a choice of treatments.

Clinical management

Psoriasis can be treated with topical therapies, phototherapy, systemic non-biological therapies and systemic biological therapies

- 3.2 People with plaque psoriasis may have topical therapies first line, followed by phototherapy second line. If these treatments do not control the psoriasis, people may have systemic conventional non-biological therapies third line (such as methotrexate, ciclosporin or acitretin). If the disease does not respond to these, people may have fourth-line treatment including systemic biological therapies (such as adalimumab, etanercept, ixekizumab, infliximab, secukinumab or ustekinumab), apremilast or dimethyl fumarate, which they continue as long as the drugs work. 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. However, 1 clinical expert explained that switching treatments is likely to affect the effectiveness of subsequent drugs and, that in clinical practice, clinicians tend to avoid switching if possible. For people whose disease does not respond to multiple biological agents, apremilast or dimethyl fumarate, the only remaining treatment option is best supportive care, which usually consists of topical agents and bandaging.

Position of brodalumab in the treatment pathway

Brodalumab is most likely to be used fourth line, as an alternative to systemic biological therapies, apremilast and dimethyl fumarate

3.3 The marketing authorisation for brodalumab is for 'adults who are candidates for systemic therapy'. However, the company positioned brodalumab fourth line, as an alternative to biological therapies, apremilast and dimethyl fumarate. One clinical expert confirmed that this is the stage in therapy at which NHS clinicians would most likely use brodalumab. The committee concluded that it would appraise brodalumab as a fourth-line therapy, which is when other biological therapies, apremilast and dimethyl fumarate are current treatment options.

Clinical evidence

The AMAGINE trials provide the key clinical evidence for brodalumab

3.4 The main evidence for brodalumab came from the 3 AMAGINE trials (1, 2 and 3). These were randomised double-blind trials that included a total of 4,373 patients with plaque psoriasis. They compared 2 doses of brodalumab (140 mg [unlicensed] or 210 mg) with placebo (all trials) and ustekinumab (AMAGINE-2 and -3 only). The company submission included data only for patients randomised to the licensed 210 mg dose of brodalumab (a total of 2,915 patients had brodalumab 210 mg, ustekinumab or placebo). The primary outcomes were the Psoriasis Area and Severity Index (PASI) and the static Physician Global Assessment (sPGA). They were assessed at the end of the induction period (at 12 weeks) and differed depending on the treatment comparison:

- Compared with placebo, the co-primary outcomes were:
 - a 75% reduction in the PASI score from when treatment started (PASI 75) and
 - a rating of 'clear' (score of 0) or 'almost clear' (score of 1) on the sPGA.
- Compared with ustekinumab, the primary outcome was a 100% reduction in the PASI score from when treatment started (PASI 100), that is, complete clearance.

Patients in all 3 trials were followed up in open-label extension studies.

The population in AMAGINE is similar to patients in the NHS who may have brodalumab

3.5 The committee considered whether patients in AMAGINE were similar to those in NHS clinical practice with respect to:

- **Severity of disease:** AMAGINE included patients with 'moderate to severe' psoriasis with a PASI score of 12 or more. No minimum Dermatology Life Quality Index (DLQI) score was included. Previous NICE technology appraisals defined 'severe' and 'very severe' psoriasis based on the PASI and DLQI, and the PASI threshold for 'severe' is 10 or more. One clinical expert explained that the AMAGINE population was generally aligned to NICE's technology appraisals definition of 'severe', and he did not expect that treatment response would differ depending on whether the PASI score was 10 or 12 at baseline.
- **Stability of disease:** the committee noted that AMAGINE included people with 'stable' psoriasis for at least 6 months before randomisation. One clinical expert explained that, in trials, stable psoriasis usually means the absence of significant flares needing treatment in hospital. He advised that disease stability would be unlikely to change treatment effect.
- **Previous treatment:** the committee noted that 17% to 35% of patients in AMAGINE did not have any previous systemic therapy or phototherapy, which is inconsistent with the proposed positioning of brodalumab as a fourth-line treatment in the NHS (see [section 3.3](#)). One clinical expert explained that international trials may include patients who have not had previous treatment because of different prescribing practices across countries. The company stated that, in the 3 AMAGINE trials, similar PASI 75 response rates were reported in subgroups of patients who had previously had systemic therapy or phototherapy compared with those who had not. The committee noted that these analyses were likely not powered to detect differences between subgroups. It recalled that previous treatment could change the effectiveness of subsequent therapy (see [section 3.2](#)).

The committee concluded that, although the results from the overall AMAGINE population may have overestimated the clinical effectiveness of brodalumab because some patients in the trials had not had any previous systemic therapy or phototherapy, patients in the trials generally reflected those who would be treated with brodalumab in NHS clinical practice.

Brodalumab is more clinically effective than placebo and ustekinumab

- 3.6 The committee noted that patients randomised to brodalumab were clinically and statistically significantly more likely to achieve PASI 75 and sPGA 0 or 1 response rates at week 12 compared with placebo and ustekinumab. The committee concluded that brodalumab was more clinically effective than placebo and ustekinumab.

Brodalumab ranks high in the probability of achieving a PASI 75 response in the company's base case and sensitivity analyses

- 3.7 The company's base-case network meta-analysis indirectly compared brodalumab with adalimumab, apremilast, dimethyl fumarate, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab, using data from 59 trials (28,346 people). The base-case results showed that brodalumab had the second highest probability after ixekizumab of achieving a PASI 75 response. The company also included the results of 5 sensitivity analyses:

- Sensitivity analysis 1: this included the licensed doses.
- Sensitivity analysis 2: this used results at 16 weeks after starting treatment (rather than 12 weeks as in the base case) from 1 trial, 'CLEAR' (secukinumab compared with ustekinumab).
- Sensitivity analysis 3: this excluded trials with fewer than 100 patients.
- Sensitivity analysis 4: this excluded trials in which more than 30% of patients had had previous biological therapies.
- Sensitivity analysis 5: this excluded trials with a mean baseline PASI score greater than 25.

The ERG explained that the results from the sensitivity analyses compared with the base case were similar, but that it preferred the base case because it included more trials. The committee noted that sensitivity analysis 2 had the same number of trials and showed less statistical variation in the baseline risks for the populations across the trials compared with the base case (average between-study standard deviation was 131.9 in sensitivity analysis 2 versus 141.8 in the base case). However, it acknowledged that brodalumab was ranked consistently high in the base case and all the sensitivity analyses.

The ERG's 'placebo-adjusted' model is the preferred model

3.8 The company identified differences in PASI response rates in the placebo groups of 49 trials included in its network meta-analysis. It explored the impact of adjusting for this variation but preferred an unadjusted model for its base case because it provided a better fit to the data; this was based on a marginally lower deviance information criterion. The ERG agreed that placebo PASI response varied markedly, noting that the PASI 50 response rates ranged from 5% to 33% across trials. It explained that the variation resulted from trials that differed in design, eligibility criteria, previous treatment and other characteristics at baseline, which may have influenced the relative efficacy of the intervention to placebo. Because of this, the ERG preferred the analysis that adjusted for the variation in response rates in the placebo groups across trials to the unadjusted analysis. It made minor revisions to the company's placebo-adjusted analysis, which resulted in the same treatment rankings as the company's unadjusted base-case analysis. One clinical expert confirmed that the treatment rankings from the company's and ERG's analyses appeared valid. The committee agreed that there was variation in the placebo response rates, and that adjusting for these differences could reduce unexplained variation between studies and improve the precision of the PASI response rate estimates. The committee preferred the adjusted model for decision-making and concluded that, with adjustment, brodalumab remained ranked among the top few treatments in terms of PASI response rate.

Company's economic model

The model has a Markov state transition structure

3.9 In its Markov state transition model used to assess the cost effectiveness of brodalumab, the company assumed that treatments improved quality of life but did not extend length of life. The model contained 4 health states: induction, maintenance, best supportive care and death. All patients entered the model in the induction state and had the first treatment in a given sequence (see [section 3.10](#)). They moved from the induction state to the maintenance state if they had at least a PASI 75 response measured at the end of induction. From there, some patients could stop treatment for any reason and move onto the next treatment in the sequence. Patients who did not have a PASI 75 response moved onto the induction phase of the next treatment in the sequence. Patients moved into the best supportive care state between treatments in a sequence or if their

psoriasis did not respond to the last active treatment in a sequence. All patients could move into the death state at any time.

The company compared 9 treatment sequences in the model

3.10 The company's decision problem compared a sequence of treatments including brodalumab with 8 other treatment sequences excluding brodalumab. Each sequence comprised 4 treatments:

- The first treatment was either brodalumab, another biological therapy (adalimumab, etanercept, infliximab, ixekizumab, secukinumab or ustekinumab), apremilast or dimethyl fumarate.
- The second treatment was ustekinumab, except in the sequence in which ustekinumab was used as the first treatment; in that sequence, adalimumab was used as the second treatment.
- The third treatment was secukinumab, except in the sequence in which secukinumab was used as the first treatment; in that sequence, adalimumab was used as the third treatment.
- The fourth treatment in all sequences was best supportive care.

The company chose these sequences based on expert advice and reported drug use in the British Association of Dermatologists registry. One clinical expert advised that these sequences generally reflected NHS practice and the NICE-accredited guidelines on biological therapy for psoriasis from the British Association of Dermatologists (2017). The committee was aware that additional factors should be considered when comparing treatment sequences rather than individual treatments, such as the optimal ordering of treatments and the impact of including treatments that may not be cost effective. The committee agreed that, in principle, it was appropriate to compare treatment sequences in this appraisal, and that the sequences chosen by the company broadly reflected NHS clinical practice.

Assumptions in the economic model

A general treatment stopping rate is acceptable for decision-making

3.11 The company assumed in its model that 18.7% of patients in the maintenance phase stop treatment every year for any reason and move onto the next

treatment in the sequence. The clinical experts advised that the treatment stopping rate appeared reasonable. The committee preferred the company to use treatment-specific stopping rates, but understood that there were not enough data. It agreed that the company's assumption about the rate of stopping treatment was acceptable for decision-making.

The impact of switching treatment on the effectiveness of a drug is uncertain

- 3.12 The company assumed in its model that a given treatment is equally effective regardless of its position in a sequence. One clinical expert explained that this is unlikely to be the case because a treatment given fourth in a sequence would likely be less effective than the same treatment given earlier on. However, he explained that there is currently no evidence to show the extent to which effectiveness of treatments changes when used at different stages in therapy. The company conducted subgroup analyses of patients previously treated and untreated (see [section 3.5](#)), but no evidence was presented that showed how treatment effects changed at different positions in a given sequence. The committee concluded that it is clinically plausible that the effectiveness of a drug would change depending on its position in a treatment sequence. However, without robust supporting evidence for this, it accepted the company's assumption of equal treatment effect at any point in a given sequence.

Mortality rates adjusted for increased risk of death from psoriasis are appropriate

- 3.13 The company modelled the rate at which patients died in the model using age and sex-specific annual mortality rates from the general UK population, adjusted for the increased risk of death in patients with moderate to severe psoriasis relative to matched controls based on the UK GPRD study (hazard ratio 1.42, 95% confidence interval 1.25 to 1.62). The committee was aware that the increased risk was likely related to co-morbid conditions commonly associated with severe plaque psoriasis, and that treating psoriasis in itself would not extend life. The ERG explained that, because the risk of death was the same for all treatments, the mortality assumptions affected how long people lived in the model (that is, whether they lived long enough to have all 4 treatments in the sequence). The committee concluded that the company's approach to modelling mortality reflected the best available evidence.

Utility values in the economic model

Utility values adjusted for baseline EQ-5D are preferable to those adjusted for baseline DLQI

3.14 To estimate how much brodalumab improves quality of life, the company used data from a subgroup of patients from AMAGINE-1 who had a DLQI of greater than 10, stratified by PASI response levels and adjusted for baseline DLQI. It further adjusted the utility values for serious adverse events. The ERG preferred utility values adjusted for baseline EQ-5D, rather than baseline DLQI, because the regression model adjusting for baseline EQ-5D provided a better fit of the data. One clinical expert explained that the DLQI lacks sensitivity and tends to underestimate the quality of life of patients with chronic psoriasis. The committee concluded that utility values adjusted for baseline EQ-5D were more appropriate than those adjusted for baseline DLQI.

Costs in the economic model

The ERG's cost estimates are preferable to the company's

3.15 The ERG made the following changes to the company's base case:

- Brodalumab: the ERG costed 8 doses rather than the company's 7 doses because unit packs of 2 doses cannot be split.
- For people whose disease does not respond to treatment and who have another treatment: the ERG applied a cost of £128 per 2-week cycle in line with previous NICE technology appraisals; the company assumed that this cost is already included in the costs of 'best supportive care'.
- Extra monitoring for dimethyl fumarate: the ERG included the cost for 2 additional outpatient visits and associated blood tests, applied as described in dimethyl fumarate's summary of product characteristics.

The committee agreed that the ERG's adjustments to costs in the model were appropriate.

Cost-effectiveness estimate

Treatment sequences including drugs that are not cost effective may result in

misleading cost-effectiveness estimates

- 3.16 The committee was aware that treatment sequences, although more likely to reflect clinical practice, may provide misleading cost-effectiveness estimates of brodalumab. This is because the company chose a limited number of treatment sequences and positions within these sequences. The cost effectiveness of any new treatment included early in these sequences would likely be driven by avoiding more expensive and potentially cost-ineffective subsequent treatments and best supportive care. Therefore, moving the position of the treatment within a sequence would affect which therapies patients have afterwards, and hence the cost effectiveness of treatment. Ideally, the committee would have liked to see all plausible sequences modelled in a fully incremental analysis taking into account different treatment positions and sequence lengths. Furthermore, the use of sequences may include treatments that are not cost effective. The committee was aware that, although previous NICE technology appraisals considered biological treatments, apremilast and dimethyl fumarate to be a cost-effective use of NHS resources, variation in model structure and inputs across appraisals may result in differences in cost-effectiveness estimates. The committee noted that the ERG compared individual treatments with best supportive care in its own base case, setting the second and third options in all sequences to best supportive care. The committee concluded that it would consider comparisons of individual treatments with best supportive care in its decision-making to account for potential bias from including non-cost-effective comparators in sequences.

Brodalumab is cost effective compared with other biological treatments, apremilast and dimethyl fumarate for people with severe psoriasis

- 3.17 The committee considered whether brodalumab would be a cost-effective use of NHS resources for people with severe psoriasis for whom treatment with biological treatments, apremilast or dimethyl fumarate is an option, taking into account the patient access schemes associated with apremilast, ixekizumab and secukinumab. The committee considered the probabilistic results from the company's base case for pairwise comparisons of brodalumab in a sequence with other biological treatments, apremilast and dimethyl fumarate in a sequence. The results showed that the brodalumab sequence either dominated (was more effective and less costly) or had incremental cost-effectiveness ratios that were less than £25,000 per quality-adjusted life year (QALY) gained compared with other biological treatments, apremilast and dimethyl fumarate in

a sequence. The committee then considered the results of the ERG's base case that compared individual treatments with best supportive care, given the potential for biased cost-effectiveness estimates in the company's model (see [section 3.16](#)). This analysis used the ERG's 'placebo-adjusted' network meta-analysis (see [section 3.8](#)), utility values adjusted for baseline EQ-5D (see [section 3.14](#)), and revisions to cost assumptions in the model (see [section 3.15](#)), all which were modifications that the committee accepted. The ERG's analyses also showed that brodalumab was cost effective. The similarity between the company's and ERG's results reassured the committee that the model produced robust estimates. The committee concluded that it could recommend brodalumab as an option for treating severe chronic plaque psoriasis that has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or when these options are contraindicated or not tolerated.

Brodalumab should be stopped if there is an inadequate response at 12 weeks

3.18 Previous NICE technology appraisals for treating psoriasis have recommended stopping treatment if there is an inadequate response; an adequate response is defined as either a 75% reduction in the PASI score from when treatment started, or a 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started. The committee agreed that, if there was an inadequate response to brodalumab, the patient should stop treatment. It noted that PASI 75, assessed 12 weeks after starting treatment, was the primary outcome in the trial data used to model the cost effectiveness of brodalumab. The committee therefore concluded that brodalumab should be stopped if there is an inadequate response at 12 weeks, with an adequate response as defined in previous NICE technology appraisals.

Other factors

The company did not submit evidence for people with less severe psoriasis limited to the face, hands, feet and genitals

3.19 People with psoriasis at sites that particularly impact quality of life, such as the face, hands, feet and genitals, may not meet the PASI threshold used to define 'severe' in NICE technology appraisals, and so would not be eligible for fourth-line treatment (that is, their psoriasis may not cover a large enough part of their body to qualify for treatment). The committee agreed that this in itself was not

an equality issue. It was also aware that the company submitted no evidence to enable it to make a separate recommendation for treating patients with psoriasis confined to these specific sites that has been defined as less severe (that is, a PASI lower than 10).

The PASI and DLQI may not be appropriate for all people with psoriasis

3.20 The committee noted, as in previous NICE technology appraisals on psoriasis, potential equality issues:

- the PASI might underestimate disease severity in people with darker skin
- the DLQI has limited validity in some people, and may miss anxiety and depression.

The committee concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate. Also, it concluded that, when using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

Innovation

3.21 The committee understood that brodalumab targets the same pathway as, but has a different mechanism of action from, other interleukin-17 inhibitors; it targets a different part of the pathway. However, the committee concluded that, without evidence on the benefit of targeting a specific part of the pathway, there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4 Implementation

- 4.1 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.
- 4.2 The Welsh ministers have 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 2 months of the first publication of the final appraisal determination.
- 4.3 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 plaque psoriasis and the doctor responsible for their care thinks that brodalumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 4.4 The Department of Health and Leo Pharma have agreed that brodalumab 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 ukmarketaccess@leo-pharma.com (01844 347 333).

5 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), a technical adviser and a project manager.

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Accreditation

