NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lanadelumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: June 2019

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using lanadelumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 19 July 2019

Second appraisal committee meeting: 07 August 2019

Details of membership of the appraisal committee are given in section 5.

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1 Recommendations

1.1 Lanadelumab is not recommended, within its marketing authorisation, for routine prevention of recurrent attacks of hereditary angioedema in people aged 12 years and older.

1.2 This recommendation is not intended to affect treatment with lanadelumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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. This decision should be made jointly by the clinician and the young person and/or the young person's parents or carers.

Why the committee made these recommendations

People with hereditary angioedema experience attacks which are often unpredictable and lead to swellings in various locations on the body. Although its marketing authorisation covers the full treatment pathway, the company positioned lanadelumab for the population currently eligible for long-term prophylactic C1-INH in the current NHS England commissioning policy. C1-INH is the most appropriate comparator for the company's proposed positioning.

Evidence from a randomised controlled trial comparing lanadelumab with placebo with short follow up suggests that people having lanadelumab have fewer hereditary angioedema attacks compared with placebo. There are no data directly comparing lanadelumab with C1-INH therefore a small cross-over trial comparing Cinryze (a C1-INH) with placebo was used to estimate the relative effectiveness of lanadelumab and C1-INH indirectly.

Lanadelumab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. In line with its summary of product characteristics, a lower dosing frequency of lanadelumab (once every 4 weeks) could be used if disease is stably attack-free, but there is currently

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no evidence that includes switching to this lower dosing frequency and this has a large impact on the cost-effectiveness estimates. Similarly, the dose per administration, and therefore the cost, of C1-INH has a large impact on the estimates of cost effectiveness, and it is unclear what dose of Berinert (a C1-INH) is used in clinical practice. Furthermore, the discounted price of C1-INH treatments paid by the NHS is not currently included in the cost-effectiveness results. Therefore, all estimates of cost effectiveness for lanadelumab compared with C1-INH are highly uncertain. Because some cost-effectiveness estimates that were considered clinically plausible are substantially higher than what NICE normally considers an acceptable use of NHS resources, lanadelumab cannot be recommended for routine use in the NHS.

2 Information about lanadelumab

Marketing authorisation indication	Lanadelumab (Takhzyro, Shire) is indicated for routine prevention of recurrent attacks of hereditary angioedema in patients aged 12 years and older.
Dosage in the marketing authorisation	The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight. It is administered as a subcutaneous injection.
Price	The list price for lanadelumab is £12,420 per 300 mg vial. The company has a commercial arrangement (simple discount patient access scheme), which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Shire (now part of Takeda), a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that none of the key issues identified in the technical report were resolved during the technical engagement stage. It recognised

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that there were areas of uncertainty associated with the analyses presented (see technical report, issues 1 to 4), and took these into account in its decision making. It discussed the following issues (issues 1 to 4) which were outstanding after the technical engagement stage.

New treatment option

There is an unmet need for more effective treatment options

3.1 Hereditary angioedema is a rare genetic disorder which usually develops in childhood or early adulthood and is associated with the build up of excessive fluid (oedema) causing localised swellings. The swellings usually happen in the mouth, gut or airway and can cause severe pain. Swelling of the airways can be life threatening. The patient experts described how swellings can reach a very large size quickly (30 to 40 minutes) and can take over 2 days to resolve. The patient experts explained that this can have a substantial impact on quality of life, particularly because attacks are often difficult to predict. The clinical experts explained that attacks can be triggered by anxiety and stress, for example caused by exams, surgery or dental treatment as well as positive life events such as weddings and holidays. The clinical experts advised that in clinical practice, people who have regular attacks and those who are at risk of severe swelling would benefit from long-term prophylactic treatment. The clinical experts explained that long-term prophylactic treatment with an intravenous C1 esterase inhibitor (C1-INH) is currently only available for a small subgroup of people meeting the criteria set out in the NHS England commissioning policy (see section 3.2). They also emphasised that current oral long-term prophylactic treatment, such as attenuated androgens, is used earlier in the treatment pathway, is associated with side effects and has limited effectiveness (see section 3.3). The patient and clinical experts suggested that being able to control symptoms in the long term may reduce anxiety and thereby reduce attacks. The committee concluded that there is an unmet need for more effective treatment options.

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Treatment pathway and comparators

The company's proposed positioning of lanadelumab, for people currently eligible for long-term prophylactic C1-INH, is appropriate

3.2 After technical engagement, the company positioned lanadelumab for the population currently eligible for long-term prophylactic C1-INH in the NHS England commissioning policy. The policy includes people with 2 or more clinically significant attacks per week over 8 weeks, despite long-term oral prophylaxis, or if long-term oral prophylactic treatment is not appropriate. The committee understood that this is a narrower population than is covered by the full marketing authorisation for lanadelumab (indicated for routine prevention of recurrent attacks of hereditary angioedema in people aged 12 years and older). The clinical experts explained that the criteria used in the NHS England commissioning policy to identify people eligible for long-term prophylactic C1-INH was well defined and is currently used in clinical practice. The committee accepted the company's positioning of lanadelumab and agreed to take this into account when making its recommendations.

C1-INH is the most appropriate comparator at the company's proposed positioning of lanadelumab

3.3 The company considered C1-INH to be the only relevant comparator because it had positioned lanadelumab for people who are currently eligible for long-term prophylactic C1-INH (see section 3.2). The company used a blended C1-INH comparator that included Berinert and Cinryze because, according to clinical advice, these were the most commonly used C1-INH treatments. The clinical experts explained that the use of individual C1-INH varied between different treatment centres, but agreed that Berinert and Cinryze were the most commonly used, with a third C1-INH treatment, Ruconest, being used very rarely in practice. The committee was aware that Berinert is only licensed to treat acute attacks but the clinical experts advised that it is also used in clinical practice as a long-term prophylactic treatment. The clinical experts clarified that acute

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(on-demand) treatment with C1-INH can be similar to long-term prophylactic C1-INH (as described in the NHS England commissioning policy) if on-demand treatment is given frequently (for example, several times per week). Following clinical expert opinion during technical engagement that lanadelumab could be used earlier in the treatment pathway than C1-INH, the company submitted new evidence comparing lanadelumab with long-term prophylactic oral treatment, which is used earlier in the treatment pathway (the results are confidential and cannot be reported here). The committee also understood that there was no trial evidence for oral therapy and therefore agreed it was not an appropriate comparator for the company's proposed positioning of lanadelumab. The clinical experts explained that most people who are eligible for long-term prophylactic C1-INH would choose to have it. Those choosing not to have it would still have acute treatment during an attack. The committee concluded that C1-INH is the only comparator for the company's proposed positioning of lanadelumab.

Clinical evidence

The full HELP-03 population and the subgroup with 8 or more attacks over 4 weeks at baseline are relevant for decision making, but the latter is less robust

3.4 The clinical evidence for lanadelumab comes from HELP-03, a phase 3 randomised controlled trial. It compared 3 dose schedules of lanadelumab with placebo in 125 people aged 12 years or older with type I or II hereditary angioedema who had at least 1 attack in the subsequent 4 weeks. The committee understood that the frequency of attacks in the trial inclusion criteria was lower compared with the company's proposed positioning, which specified at least 2 or more attacks per week (see section 3.2). The committee considered that the HELP-03 trial population had less severe disease, on average, than the population currently eligible for C1-INH in the NHS. The company reported a scenario analysis using a subgroup of the full HELP-03 population with a baseline risk of 8 or more attacks over 4 weeks, which is the same attack frequency (2 per week) as

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the criteria in the NHS England commissioning policy. The ERG explained that this analysis was based on very few patients (exact data are confidential and cannot be reported here) so may not be robust. In response to technical engagement, the company also submitted analyses from HELP-03 showing no difference in time to first attack after reaching an attack-free 'steady state' with lanadelumab (that is from day 70 onwards) in people with fewer than 3 attacks per month at baseline compared with people having 3 or more attacks per month). The ERG noted that this evidence was not consistent with the criteria set out by NHS England because it used a threshold of 3 attacks per month rather than 8. The clinical experts clarified that they would expect response rates with lanadelumab to be the same, irrespective of the number of attacks at baseline. The committee concluded that the trial results were generalisable to the population that would use lanadelumab within the NHS. It also concluded that both the full HELP-03 population and the subgroup with 8 or more attacks at baseline were relevant, but that the latter was less robust because it was based on very few patients.

There is no long-term evidence on the use of lanadelumab at its lower dosing frequency

3.5 The HELP-03 trial used 2 different dosing schedules of the licensed dose of lanadelumab (300 mg): every 2 weeks (high frequency) and every 4 weeks (low frequency). The committee noted that the lanadelumab summary of product characteristics states that the low frequency dosing schedule could be used in 'patients who are stably attack free, especially in patients with low weight.' The HELP-03 trial did not allow switching between the dosing schedules and treatment continued on the same dose for 26 weeks. The committee was aware that longer-term evidence was being collected by the HELP-04 open-label extension study that included people who rolled-over from HELP-03 and other people who met the inclusion criteria but had not taken part in HELP-03 (non-rollover). The committee understood that only the high dosing frequency of lanadelumab was used in HELP-04 and noted that data from HELP-04 was not used in

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the model. At the appraisal committee meeting, the company advised that 3 ongoing studies (1 in the USA, 1 in Europe and 1 in France) were collecting data on the lower frequency dosing schedule, but the earliest data would become available during mid-2020. The committee concluded that there is uncertainty around the long-term use of lanadelumab at the low dosing frequency because the HELP-04 extension study did not include this dose.

The indirect treatment comparison should be used to estimate the treatment effect for lanadelumab and C1-INH

3.6 HELP-03 compared lanadelumab with placebo and no evidence was identified that compared lanadelumab with C1-INH directly. Therefore, the company did an indirect treatment comparison using the HELP-03 trial and a cross-over trial (CHANGE) of 22 patients comparing C1-INH with placebo. The company used a Bayesian indirect comparison with a fixed effects model, stating that a random effects model would not be robust because of the small sample size. The ERG explained that they were not able to validate the company's inputs for the indirect treatment comparison but broadly agreed with the company's approach. The committee understood that the company's revised base case used data from HELP-03 to inform the attack rate in the lanadelumab arm and results from the indirect comparison to inform the attack rate in the C1-INH arm. The ERG explained that the company's approach predicted a larger reduction in attacks for lanadelumab, compared with C1-INH, than the indirect comparison predicted (exact data is confidential so not reported here). The committee considered both approaches and concluded that using the indirect treatment comparison to inform attack rates for both lanadelumab and C1-INH is the more consistent and robust approach. The committee concluded that the indirect treatment comparison should be used to estimate the treatment effect for both lanadelumab and C1-INH.

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Lanadelumab is clinically effective compared with C1-INH

3.7 Results from HELP-03 showed that both the high and low lanadelumab dosing frequencies significantly reduced mean monthly attack rates compared with placebo, by 87% and 73% respectively ($p<0.001$). The company's indirect treatment comparison produced very similar results for lanadelumab compared with placebo. It also showed that both dosing frequencies of lanadelumab had lower mean attack rates compared with C1-INH (exact data is confidential so cannot be reported here). The committee concluded that lanadelumab is clinically effective compared with C1-INH.

Cost effectiveness

The company's model is acceptable for decision making

3.8 The company submitted a cohort-level partitioned survival model with 2 health states; alive and dead. The alive health state was split into an attack-free or attack period. The model used the average duration of attack to estimate the time spent in the attack-free and attack period in each cycle. The committee understood that attack severity was not modelled explicitly, but that a single disutility and treatment cost was applied per attack to reflect a typical attack severity. The model used data from the full HELP-03 population and the committee recalled that it considered the trial population to be generalisable to people who would have treatment in the NHS (see section 3.4). The committee noted that the model did not include a survival benefit for lanadelumab compared with C1-INH. The patient experts noted that data from the Office of National Statistics showed there were 5 deaths because hereditary angioedema in 2017. The committee agreed that it is plausible that there may be a very small survival benefit associated with lanadelumab in practice, but it had not seen evidence to support this. The committee concluded that the company's model was acceptable for decision making, though the indirect treatment comparison should be used to model relative effectiveness (see section 3.6).

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Subsequent treatment

Treatment discontinuation data from HELP-03 are acceptable for decision making

3.9 In its revised base case, the company assumed that 91% of people taking lanadelumab would continue to take it for a lifetime. This was based on 91% of patients completing treatment in HELP-03. The committee recalled that the treatment period in HELP-03 was 26 weeks and was concerned that more people would stop lanadelumab over a longer follow-up period. Following technical engagement, the company submitted new interim data from the ongoing HELP-04 study that showed only 6% of patients had stopped over 15 months. The committee concluded it was reasonable to use discontinuation rates from HELP-03 because the results were similar to longer-term data from HELP-04.

It is plausible to assume that people who stop lanadelumab will start C1-INH and those having C1-INH will continue to have it for a lifetime

3.10 The company's revised base case assumed that if treatment is stopped in the lanadelumab arm, people would go on to have treatment with C1-INH. The company also assumed that people in the C1-INH arm would continue to have treatment over a lifetime. The clinical experts confirmed that in clinical practice, there are no alternative treatment options after C1-INH therefore people having long-term prophylactic C1-INH were unlikely to stop treatment altogether. The clinical experts also advised that if lanadelumab was stopped, it was likely that C1-INH treatment would be started because it would become the only available treatment. The committee concluded that it was clinically plausible to assume that people who stop lanadelumab will start C1-INH and those having C1-INH will continue to have it for a lifetime.

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Continued treatment effect of lanadelumab

A continued treatment effect for lanadelumab is clinically plausible for most people, but assuming a continued treatment effect for all people is optimistic

3.11 The company's revised base case assumed that the effectiveness of lanadelumab would persist over time in all patients who continue to have treatment. The clinical experts advised that similar to other biological therapies, it would be clinically plausible to assume that a small proportion (5 to 10%) of people would develop non-response to lanadelumab over time. The committee understood that the company's model did not account for this small proportion who may develop non-response. The committee concluded that a continued treatment effect for lanadelumab is clinically plausible for most people, but there is a small proportion of people who may develop non-response over time. It also concluded that the estimates of cost effectiveness for lanadelumab would be optimistic because the model did not include this non-response.

C1-INH use

It is plausible to assume 50% to 75% of people having C1-INH will have Berinert and the rest will have Cinryze

3.12 In its revised base case, the company assumed that between 50% to 75% of people having C1-INH will have Berinert instead of Cinryze (the exact data is confidential and cannot be reported here). The company based this on hospital dispensing data from the Hospital Pharmacy Audit over a 3-month period but also reported 3-year data that showed the proportion of Berinert use was always higher than 50% (exact data is confidential and cannot be reported here). The clinical experts stated that C1-INH use varied in clinical practice but Berinert and Cinryze were likely to be used in approximately equal proportions. The clinical and patient experts described current supply issues with both Berinert and Cinryze, and advised that people may prefer to use Berinert because it was the first C1-INH to become available and many people have experience using it. The

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committee recalled that the clinical experts advised that Ruconest was rarely used in practice (see section 3.3). The commissioning expert from NHS England explained that data had been collected on the use of the NHS England commissioning policy which showed around 73% of people have Berinert currently, but noted that this was more evenly split before recent supply issues with Cinryze. The commissioning expert also advised that the NHS pays lower prices for C1-INH treatments than their current list prices, which were the prices used in the model. The committee concluded that it is reasonable to assume between 50% and 75% of people having C1-INH will have Berinert, and the rest will have Cinryze, but noted it had not yet seen cost-effectiveness results using the discounted price for C1-INH treatment.

Dosing and dose reduction

There is substantial uncertainty around the dosing schedule for Berinert and a fixed dose is clinically plausible

3.13 The company assumed that people having Berinert had a dose that varied by weight (the exact dose is confidential and cannot be reported here), whereas the licensed dose of Cinryze is 1,000 IU every 3 or 4 days for the routine prevention of angioedema attacks. The committee recalled that Berinert was not licensed for long-term prophylaxis but was used in clinical practice (see section 3.3) and noted that its summary of product characteristics recommended a dose of 20 IU per kilogram of body weight to treat an acute attack. The clinical experts explained that in clinical practice Berinert may be under or over-dosed to avoid wastage, for example a weight-based dose of 1,100 IU may be under-dosed to 1,000 IU so that 2 full vials are used instead of 3. The committee recognised that the company's preferred weight-based dose of Berinert was substantially higher than 1,000 IU per day (the exact dose is confidential and cannot be reported here). The ERG noted that the trial used in the indirect treatment comparison for C1-INH (CHANGE) used a 1,000 IU dose of Cinryze only. The ERG also identified a publication using

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Berinert patient registry data from 47 patients in the US and Europe having long-term prophylaxis which reported a median dose of 1,000 IU (range 500 to 3,000 IU). The committee was aware that the ERG scenario analyses using a fixed 1,000 IU dose of Berinert substantially increased the cost-effectiveness estimate for lanadelumab in both the full HELP-03 population and the subgroup with at least 8 attacks per month. The committee noted that it had not seen data on C1-INH dosing collected to monitor treatment against the NHS England commissioning policy. It concluded that there is substantial uncertainty around the dosing schedule for Berinert but that a rounded fixed dose of 1,000 IU is the mostly likely to reflect NHS practice.

There is substantial uncertainty around the proportion of people having the lower dosing frequency of lanadelumab, but 77% would be the maximum

3.14 The company assumed that 77% of people having lanadelumab would have the lower frequency dose (once every 4 weeks) after 1 year. The company reasoned that this was plausible because it was the proportion of patients in HELP-03 having the higher dose frequency of lanadelumab and who were attack free between days 70 and 182 (a period of just under 4 months). It explained that in practice, it would be appropriate to reduce the lanadelumab dosing frequency in these people, as specified in its summary of product characteristics. The ERG clarified that changes to dosing frequency were not allowed in HELP-03, therefore the proportion used by the company was based on people who would have been eligible to reduce their dosing frequency in practice, but did not actually do so as part of the trial. The committee recalled that the HELP-04 study did not include the lower dosing frequency of lanadelumab, therefore there is a lack of long-term evidence around the use of this dosing schedule (see section 3.5). The clinical experts explained that it was clinically plausible that 77% of people would have their dosing frequency reduced, though noted that this is difficult to predict. Other responses at technical engagement also noted that given the nature of the disease, attack rates vary over a lifetime and even if dosing frequency is increased, it is often

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lowered again in the future. The patient experts described how people may wish to use the lowest effective dose to avoid repeated administration of intravenous C1-INH. The committee noted that ERG scenario analyses assuming 50% had the lower dosing frequency of lanadelumab substantially increased the cost-effectiveness estimate in both the full HELP-03 population and the subgroup with at least 8 attacks over 4 weeks. Given the lack of long-term data on the low dosing frequency of lanadelumab and the large impact on the cost-effectiveness results, the committee was not convinced that 77% was plausible. The committee reasoned that 77% was likely to be an upper limit, because a reduction in dosing frequency would only be considered in people who are attack free, and some of those people might choose not to reduce their dosing schedule while the higher frequency dosing was controlling attacks. The committee agreed that it could not estimate a lower bound to this value, therefore the true value would be between an unrealistic minimum of 0% and a maximum of 77%. The committee concluded that there is substantial uncertainty around the proportion of people having the lower dose frequency of lanadelumab, and 77% is the upper limit on this value.

Health-related quality of life

The company's preferred utility values are acceptable for decision making

3.15 The company used utility values from Nordenfelt (2014), a Swedish study that included EQ-5D-5L values for both the attack-free and attack health states. The company also added a utility benefit for subcutaneous administration of lanadelumab, compared with intravenous C1-INH. The committee understood that EQ-5D-5L values were collected in HELP-03 but this was limited to 3 fixed time-points (days 0, 98 and 182). For this reason, the company explained that the utility values collected in HELP-03 were limited and could not be used in the model. The ERG acknowledged that an alternative data source to the trial would be needed to measure the quality of life decrement during an attack, because only 2 of the 807

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recorded attacks in HELP-03 had completed EQ-5D data. The committee considered the company's approach to utility values and noted that the ERG had not changed this in its preferred analysis. It concluded that the company's preferred utility values that included a benefit for lanadelumab subcutaneous administration were acceptable for decision making.

End of life

Lanadelumab does not meet the criteria to be considered a life-extending treatment at the end of life

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It noted that lanadelumab is a long-term prophylactic treatment and that the company did not make a case for lanadelumab to be considered a life-extending treatment. The committee was aware that the company's revised base case showed no difference in the modelled mean survival for lanadelumab compared with C1-INH despite the very small survival benefit associated with lanadelumab (see section 3.8). However, based on the evidence presented, the committee concluded that lanadelumab does not meet the criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness results

The company's revised base case is not suitable for decision making

3.17 The company submitted a revised base case after technical engagement that showed lanadelumab was dominant (that is less costly and more effective) compared with C1-INH. The committee noted that this did not include all its preferred assumption because it used data from HELP-03 to estimate the treatment effect of lanadelumab rather than results from the indirect treatment comparison (see section 3.6). It also noted that the revised base-case analyses were based on the full HELP-03 population only, and not the subgroup with 8 or more attacks in the previous

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4 weeks. The committee concluded that the company's revised base case included the full HELP-03 population only and did not include all its preferred assumptions. Therefore it was not suitable for decision making.

The estimates of cost effectiveness are considerably uncertain, and for some clinically plausible scenarios they are substantially higher than £30,000 per quality-adjusted life year (QALY) gained, therefore lanadelumab cannot be recommended

3.18 The committee considered all estimates of cost effectiveness for lanadelumab compared with C1-INH that used its preferred assumptions, that is:

- considering both the full HELP-03 population and the subgroup of people with at least 8 attacks in the previous 4 weeks at baseline (see section 3.4)
- using the indirect treatment comparison to estimate the treatment effect for lanadelumab and C1-INH (see section 3.6)
- using discontinuation rates from HELP-03 (see section 3.9)
- assuming C1-INH is a subsequent treatment if lanadelumab is stopped, and C1-INH that is continued over a lifetime (see section 3.10)
- assuming a continued treatment effect for lanadelumab (see section 3.11)
- assuming between 50% to 75% of people having C1-INH will have Berinert (see section 3.12).

However, it recalled substantial uncertainty around the dose of Berinert and the proportion having the lower dose frequency of lanadelumab in the long term (see sections 3.13 and 3.14). It was aware that NHS England had collected some data on the use of long-term prophylactic C1-INH that is currently being used according to the NHS England clinical commissioning policy. However, the committee noted it had not seen these data and therefore could not assess how it would impact the cost-effectiveness results.

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The committee noted that the company's revised base-case estimate of cost effectiveness showed lanadelumab was dominant compared with C1-INH, but noted that for other clinically plausible scenarios it was substantially higher than £30,000 per QALY gained for both populations. The committee understood that the QALY gain for lanadelumab was small, meaning the cost-effectiveness results changed dramatically between different clinically plausible scenarios. The committee specifically noted that the estimate of cost effectiveness was £1,463,662 per QALY gained in the full HELP-03 population if Berinert was assumed to be given as a fixed dose of 1,000 IU, which it considered clinically plausible (see section 3.13). It also noted that this estimate would be higher if fewer people taking lanadelumab had the lower dosing frequency in the long term, because it considered 77% to be the upper limit on this value (see section 3.14), but noted it had not seen the cumulative impact of clinically plausible scenario analyses on cost effectiveness. Based on the evidence presented to it, the committee concluded that the cost-effectiveness estimates are considerably uncertain, and for some clinically plausible scenarios are substantially higher than £30,000 per QALY gained, therefore lanadelumab could not be recommended. The committee noted that at the next appraisal committee meeting, it would like to see analyses with its preferred assumptions that incorporate the lower price paid by the NHS for C1-INH and real-world data from NHS England about the dose and current use of Berinert (see sections 3.12 and 3.13).

Innovation

Lanadelumab is innovative but all benefits are captured in the model

3.19 The committee considered lanadelumab to be innovative because it provided an alternative subcutaneous treatment option for people with recurrent attacks of hereditary angioedema. It noted that the company added a utility benefit for subcutaneous administration of lanadelumab in its revised base case. The committee concluded that lanadelumab is

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innovative, but the relevant benefit was captured in the estimates of cost effectiveness.

Equality considerations

There are no equality issues relevant to the recommendation

3.20 The company highlighted that C1-INH treatment is based on human or animal products and may not be acceptable to some people. The clinical experts confirmed that both Berinert and Cinryze were human plasma-derived blood products and some people prefer to use Ruconest (a non-plasma-derived C1-INH based on animal products) but noted that this is not commonly used in clinical practice. The committee considered the acceptability of human plasma-derived C1-INH (Berinert and Cinryze) and non-plasma-derived C1-INH based on animal products (Ruconest). It noted that some religious groups may refuse human plasma derived products but understood that the animal-based C1-INH may be used as an alternative for these people. The committee was also aware that oral treatment such as attenuated androgens can affect a woman's fertility and are therefore not appropriate for women of child-bearing age. However, the committee noted that C1-INH was available if long-term prophylaxis with oral therapy is contraindicated, for example in pregnant women. It also understood that oral prophylaxis options are used earlier in the treatment pathway than the company's positioning of lanadelumab. Therefore, the committee concluded that this was not a relevant equalities issue.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date, in particular regarding the availability of further data about the lower dosing frequency of lanadelumab. The guidance executive will decide whether the

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technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
June 2019

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 C.

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.

Abi Senthinathan
Technical lead

Jamie Elvidge
Technical adviser

James Maskrey
Project manager (from February 2019)

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Gemma Barnacle

Project manager (from June 2019)

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