NICE National Institute for Health and Care Excellence

NICE guidance

Lanadelumab for preventing recurrent attacks of hereditary angioedema

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

1 Recommendations

1.1 Lanadelumab is recommended as an option for preventing recurrent attacks of hereditary angioedema in people aged 12 and older, only if:

- they are eligible for preventive C1-esterase inhibitor (C1-INH) treatment in line with NHS England's commissioning policy, that is, they are having 2 or more clinically significant attacks (as defined in the policy) per week over 8 weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated
- the lowest dosing frequency of lanadelumab is used in line with the summary of product characteristics, that is, when the condition is in a stable, attack-free phase (see section 2) and
- the company provides lanadelumab according to the commercial arrangement.

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. For young people, this decision should be made jointly by the clinician and the young person or the young person's parents or carers.

Why the committee made these recommendations

People with hereditary angioedema have attacks that cause severe swelling of various parts of the body. Despite long-term oral preventive therapy (such as attenuated androgens) and C1-INH treatments, some people still have frequent severe attacks.

Lanadelumab's marketing authorisation is broad and covers prevention of recurrent attacks of hereditary angioedema. But there is no trial evidence comparing lanadelumab with long-term oral preventive therapy so it cannot be used instead of this therapy. Therefore the company wants lanadelumab to be used only for people who are eligible for long-term preventive C1-INH treatments in line with NHS England's commissioning policy. So C1-INH treatments are the most appropriate comparator for the company's proposed

positioning.

Evidence from a randomised controlled trial suggests that people having lanadelumab have fewer hereditary angioedema attacks than with placebo. There are data indirectly comparing lanadelumab with C1-INHs.

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) can be used if the condition is in a stable attack-free phase. But there is no clinical trial evidence on switching to this lower dosing frequency and the proportion of patients assumed to switch has a large impact on the cost-effectiveness estimates. Although all cost-effectiveness estimates for lanadelumab compared with C1-INHs are uncertain, most are within the range NICE normally considers an acceptable use of NHS resources. Therefore, lanadelumab is recommended only for people who are eligible for long-term preventive C1-INH treatments in line with NHS England's commissioning policy. The lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics, when the condition is in a stable attack-free phase.

2 Information about lanadelumab

Marketing authorisation indication

2.1 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

2.2 The recommended starting dose is 300 mg lanadelumab every 2 weeks. The summary of product of characteristics states that 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

2.3 The list price for lanadelumab is £12,420 per 300-mg vial.

2.4 The company has a commercial arrangement. This makes lanadelumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee 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 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.

New treatment option

There is an unmet need for more effective treatment options

3.1 Hereditary angioedema is a rare genetic disorder. It usually develops in childhood or early adulthood and is associated with the build-up of excessive fluid (oedema) causing localised swelling. The swelling may 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 swelling can enlarge 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 preventive treatment. Long-term preventive 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 NHS England's commissioning policy (see section 3.2). They also emphasised that long-term preventive oral treatment, such as attenuated androgens, is used earlier in the treatment pathway but 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 therefore reduce attacks. The committee concluded that there is an unmet need for more effective treatment options.

Treatment pathway and comparators

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

3.2 After clarification, the company positioned lanadelumab for the population currently eligible for long-term preventive C1-INH treatment, in line with NHS England's commissioning policy. The policy includes people with 2 or more clinically significant attacks (as defined in the policy) per week over 8 weeks, despite long-term oral preventive treatment, or if long-term oral preventive treatment is not appropriate. The committee understood that this is a narrower population than 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 NHS England's commissioning policy to identify people eligible for long-term preventive C1-INH treatment were well defined and used in clinical practice. The committee was aware that similar criteria were used in the company's subgroup analysis from HELP-03. This included people with 8 or more attacks over the previous 4 weeks at baseline (see section 3.4). The committee accepted the company's positioning of lanadelumab and agreed to take this into account when making its recommendations.

C1-INHs are the most appropriate comparator for the company's proposed positioning of lanadelumab

3.3 The company considered C1-INHs to be the only relevant comparator because it had positioned lanadelumab for people who are currently eligible for long-term preventive C1-INH treatment (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-INHs varied between different treatment centres. But they 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 preventive treatment. The clinical experts clarified that acute treatment with a C1-INH can be similar to long-term preventive C1-INH treatment (as described in NHS England's commissioning policy) if it is offered frequently (for example, several times per week). After clinical experts explained during the technical engagement stage that lanadelumab could be used earlier in the treatment pathway than a C1-INH, the committee considered analyses comparing lanadelumab with long-term preventive 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, such as attenuated androgens, 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 a long-term preventive 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-INHs are the only comparator for the company's proposed positioning of lanadelumab.

Clinical evidence

Results from the full HELP-03 population and the subgroup having 8 or more attacks are relevant for decision making, but the latter are less robust

3.4 The clinical evidence for lanadelumab came from HELP-03, a phase 3 randomised controlled trial. It compared 3 dose schedules of lanadelumab with placebo in 125 people aged 12 or older with type I or II hereditary angioedema who had had at least 1 attack in the last 4 weeks. The committee understood that the frequency of attacks in the trial inclusion criteria was lower than 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 a

lower frequency of attacks, on average, than the population currently eligible for C1-INH treatment 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 the criteria in NHS England's 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 the technical engagement stage, the company also submitted subgroup analyses from HELP-03. These showed no difference in time to first attack after reaching an attack-free 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 who would have lanadelumab in the NHS. It also concluded that both the results for the full HELP-03 population and for the subgroup with 8 or more attacks in the last 4 weeks at baseline were relevant, but that the latter were less robust because they were based on very few patients.

There is no long-term evidence on using lanadelumab at its lower dosing frequency

3.5 HELP-03 used 2 different dosing schedules for 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'. HELP-03 did not allow switching between the dosing schedules and treatment continued at the same dose for 26 weeks. The committee was aware that longer-term evidence was being collected in the HELP-04 open-label extension study. This included people who continued from HELP-03 and other people who met the inclusion criteria but had not taken part in HELP-03. The committee understood that only the high frequency dosing schedule was used in HELP-04 and that data from HELP-04 were not used in 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 real-world data on the use of lanadelumab, including both licensed dosing schedules, but the earliest data would become available during mid-2020. The committee concluded that there was uncertainty around the long-term use of lanadelumab at the low dosing frequency because HELP-04 did not include this dose.

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

3.6 HELP-03 compared lanadelumab with placebo and no evidence was identified that compared lanadelumab with C1-INHs directly. Therefore, the company did an indirect treatment comparison using HELP-03 and a crossover trial (CHANGE) of 22 patients, comparing a 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 committee understood that the company's indirect comparison did not address uncertainty because it used a fixed effects model. The ERG explained that it was unable to validate the company's inputs (that is, estimates of treatment effect and associated standard errors) 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-INHs, than the indirect comparison predicted (exact data are 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-INHs was 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-INHs.

Lanadelumab is clinically effective compared with C1-INHs

3.7 Results from HELP-03 showed that both the high and low lanadelumab dosing

frequencies statistically 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 than a C1-INH (exact data are confidential so cannot be reported here). The committee concluded that lanadelumab is clinically effective compared with C1-INHs.

Cost effectiveness

The company's model is acceptable for decision making

3.8 The company submitted a cohort-level state-transition model with 2 health states; alive and dead. The alive health state was split into an attack-free and an attack period. The model used the average duration of an attack to estimate the time spent in the attack-free and the attack period in each cycle. The committee understood that in the company's base case, attack severity was not modelled explicitly, but that a single disutility and treatment cost was applied per attack to reflect the severity of a typical attack. The model used data from the full HELP-03 population. 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). It noted that the model did not include a survival benefit for lanadelumab compared with C1-INHs. The patient experts noted that data from the Office of National Statistics showed there were very few deaths from hereditary angioedema in 2017. The committee agreed that it was 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, although the indirect treatment comparison should be used to model relative effectiveness (see section 3.6).

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. After the technical engagement stage, 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 that 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 a C1-INH and those having a C1-INH will continue to have it for a lifetime

3.10 The company's revised base case assumed that if treatment was stopped in the lanadelumab arm, people would go on to have treatment with a 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 other treatment options after a C1-INH. Therefore, people having a long-term preventive 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 was the only available treatment. The committee concluded that it was clinically plausible to assume that people who stop lanadelumab will start a C1-INH and those having a C1-INH will continue to have it for a lifetime.

Continued treatment effect of lanadelumab

A continued treatment effect for lanadelumab is clinically plausible for most people, but assuming this for everyone is optimistic

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

C1-INH use and cost

It is reasonable to assume 73% of people having a preventive C1-INH will have Berinert

3.12 In its revised base case, the company assumed that between 50% and 75% of people having a C1-INH would have Berinert instead of Cinryze. The company based this on hospital dispensing data from the Hospital Pharmacy Audit over a 3-month period. But it also reported 3-year data that showed the proportion of Berinert use was always higher than 50% (details of the revised base case and the dispensing data are confidential and cannot be reported here). The committee understood that the prescribing data did not differentiate between acute and preventive C1-INH use. The clinical experts stated that C1-INH use varied in clinical practice but Berinert and Cinryze were likely to be used in about 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 committee recalled that the clinical experts advised that Ruconest (another C1-INH) was rarely used in practice (see section 3.3). The commissioning expert from NHS England explained that data collected as part of NHS England's commissioning policy showed that between 2017 and 2019, an average of 73% had preventive Berinert, but the proportion fluctuated year by year. It concluded that it was reasonable to assume that 73% of people having a preventive C1-INH would have Berinert.

Cost-effectiveness results including the current discounted prices for C1-INH treatments are preferred

3.13 The company's economic model used the list prices of C1-INHs, including for the cost of treating acute attacks. The commissioning expert from NHS England advised that the NHS pays lower prices for preventive and acute C1-INH treatments than their current list prices. In its response to consultation, the company considered the long-term cost-effectiveness results that included the current discounted prices for C1-INHs to be unreliable because these discounts may change. The committee acknowledged that price discounts may change over time but considered that the cost-effectiveness analyses should include the current NHS prices. It concluded that the cost-effectiveness results should include the current discounted prices for C1-INH treatment.

Dosing and dose reduction

Berinert's dosing schedule is very uncertain but the company advisory board's dosing data are suitable for decision making

3.14 The company assumed that people having Berinert had a dose that varied by their body weight (the exact dose is confidential and cannot be reported here). But for Cinryze the licensed dose is 1,000 IU every 3 or 4 days for the routine prevention of angioedema attacks. The committee recalled that Berinert was not licensed as long-term preventive therapy but was used in clinical practice (see section 3.3). It 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 the dose of Berinert may be changed to avoid wastage, for example a weight-based dose of 1,100 IU may be underdosed 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 administration (the exact dose is confidential and cannot be reported here). The ERG noted that the trial used in the indirect treatment comparison (CHANGE) used a 1,000 IU dose of Cinryze only. The ERG also identified a publication using Berinert patient registry data from 47 patients in the US and Europe having long-term preventive treatment, which reported a median dose of 1,000 IU (range 500 IU to 3,000 IU). In its response to consultation, the company reported an average weekly dose of Berinert estimated from an advisory board meeting (with 22 clinical experts working in 16 specialist centres in England and Wales). Exact data are confidential and cannot be reported here. During consultation, the UK Primary Immunodeficiency Network (UKPIN) also submitted survey results from 28 immunology centres that included 33 patients having preventive treatment with Berinert. It reported an average weekly dose of 2,781 IU per week. The ERG explained that it was unclear whether the UKPIN results accounted for dose rounding or if there was any overlap between the centres taking part in the UKPIN survey and the company's advisory board. The company explained that its revised base case still used its preferred weight-based target dose of Berinert and applied this to the average baseline bodyweight from HELP-03, rounding to the nearest 500 IU to reduce vial wastage. The committee was aware that the company's revised base case used a higher weekly dose of Berinert than the dose reported by the company's advisory board. It agreed that the average bodyweight in HELP-03, and therefore the company's base case dose, may be higher than it would be in the population who would have lanadelumab in England, given that most people with hereditary angioedema are women and the marketing authorisation includes young people (aged 12 and above). The committee noted that demographic data on the age and proportion of women patients included in the company's advisory board and the UKPIN survey were not available. But it reasoned that the company's preferred dose may not be generalisable to the NHS in England. The committee concluded that there was substantial uncertainty around the dosing schedule for Berinert, but the dosing data from the company's advisory board were suitable for decision making.

The company's scenario analysis value of 61% for the proportion

of people who would have lower frequency lanadelumab is suitable for decision making

3.15 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 frequency dose 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 for 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 in the trial. The committee recalled that HELP-04 did not include the lower dosing frequency of lanadelumab, therefore there was a lack of long-term evidence around its use (see section 3.5). The clinical experts explained that it was clinically plausible that 77% of people would have their dosing frequency reduced, although they noted that this was difficult to predict. Other responses at the technical engagement stage also noted that given the nature of the disease, attack rates vary over a lifetime and even if dosing frequency increased, it was often lowered again. The patient experts described how people may wish to use the lowest effective dose to avoid repeated administration of an intravenous C1-INH. The committee noted that the ERG scenario analyses assuming 50% had the lower dosing frequency of lanadelumab substantially increased the cost-effectiveness estimates 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 its 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. This was because a reduced dosing frequency would only be considered for people who are attack-free, some of whom might not choose to reduce their dosing schedule while the higher frequency dosing was controlling attacks. In its response to consultation, the company included a scenario analysis that assumed 61% of people had the lower dosing frequency of lanadelumab after 1 year. The committee understood that this was the midpoint of patients whose condition was stable and who were attack-free across both lanadelumab arms in HELP-03. It also noted that the company had not changed its assumption of 77% in its

revised base case. The company explained that this assumption might be conservative because clinicians could potentially consider using the lower dosing frequency of lanadelumab in people having some minor peripheral attacks. However, the committee recalled that in the summary of product characteristics, the population eligible for the lower dosing frequency of lanadelumab were in a stable attack-free phase on treatment. The committee considered that there was substantial uncertainty around the proportion of people having the lower dosing frequency of lanadelumab. It concluded that 77% was the upper limit and preferred to use the company's scenario analysis of 61% for decision making, but noted that this remains uncertain.

Health-related quality of life

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

3.16 The company used utility values from Nordenfelt (2014), a Swedish study that included EQ-5D-5L values for both the attack-free and the attack health states. The company also added a utility benefit for subcutaneous administration of lanadelumab, compared with an 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 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

3.17 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 preventive treatment and that the company did not make a case for it to be considered a life-extending treatment. The committee was aware that the company's revised base case showed no difference between the modelled mean survival for lanadelumab and C1-INHs despite the very small survival benefit associated with lanadelumab (see section 3.8). However, based on the evidence presented, the committee concluded that lanadelumab did 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 comparing lanadelumab with C1-INHs is not suitable for decision making

3.18 The company submitted a revised base case after consultation. This showed that lanadelumab was dominant (that is, less costly and more effective) compared with C1-INHs in the full HELP-03 population and in the subgroup of people with at least 8 attacks in the previous 4 weeks. However, the committee noted that this did not include all of its preferred assumptions, that is:

- 73% of people having a C1-INH will have Berinert and the rest will have Cinryze (see section 3.12)
- all cost-effectiveness results should include the current discounted costs paid by the NHS for acute and preventive C1-INH treatment (see section 3.13)
- use dosing data from the company's advisory board for Berinert (see section 3.14)
- 61% of people having lanadelumab would switch to a lower dosing frequency after 1 year (see section 3.15).

Therefore, the committee concluded that the company's revised base case was not suitable for decision making.

Lanadelumab compared with C1-INHs is mostly cost effective and is only recommended for people eligible for preventive C1-INHs

3.19 The committee firstly considered cost-effectiveness estimates for lanadelumab compared with C1-INHs for the full HELP-03 population. It noted that most estimates from the company's plausible scenario analyses were lower than £20,000 per quality-adjusted life year (QALY) gained after including the confidential price discounts for C1-INHs (exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported here). These scenarios used Berinert dosing data from the company's advisory board and assumed that 61% of people having lanadelumab switched to the lower dosing frequency. It noted that the most plausible cost-effectiveness estimate combining these preferred assumptions (see section 3.18) was also lower than £20,000 per QALY gained for the full HELP-03 population. Secondly, the committee considered all cost-effectiveness estimates for lanadelumab compared with C1-INHs for the subgroup from HELP-03 with at least 8 attacks in the last 4 weeks at baseline (that is, the population eligible for C1-INHs in NHS England's commissioning policy, see section 3.2). It noted that estimates from the company's plausible scenario analyses were lower than £20,000 per QALY gained after including the confidential price discounts for C1-INHs (exact ICERs are confidential and cannot be reported here). These scenarios used Berinert dosing data from the company's advisory board and assumed that 61% of people having lanadelumab switched to the lower dosing frequency. It noted that the most plausible cost-effectiveness estimate combining these preferred assumptions (see section 3.18) was also lower than £20,000 per QALY gained for the subgroup of people with at least 8 attacks in the last 4 weeks, and that this was lower than the estimate for the full HELP-03 population.

The committee reiterated the uncertainty in all cost-effectiveness estimates, specifically that:

- there was no evidence to support switching to a lower dosing frequency of lanadelumab (see section 3.5)

- cost-effectiveness estimates would be even higher if fewer than 61% of people switched to the lower lanadelumab dosing frequency (see section 3.15)
- the QALY gain for lanadelumab was small relative to its incremental cost, meaning the cost-effectiveness results could change dramatically between different clinically plausible scenarios.

The committee recalled the company's proposed positioning of lanadelumab (see section 3.2) and the remaining uncertainty around the proportion of people switching to the lower dosing frequency of lanadelumab (see section 3.5 and section 3.15), which it understood could lead to higher cost-effectiveness estimates. It concluded that lanadelumab could only be recommended as a cost-effective use of NHS resources:

- for the subgroup of people who are eligible for a long-term preventive C1-INH and
- using the lowest dosing frequency of lanadelumab, in line with the summary of product characteristics.

Innovation

Lanadelumab is innovative but all benefits are captured in the model

3.20 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. It recalled there may be a very small survival benefit associated with reducing hereditary angioedema attacks (see section 3.8), but it had not seen any evidence for this. The committee concluded that lanadelumab is innovative, but all relevant benefits were captured in the cost-effectiveness estimates.

Equalities considerations

There are no equalities issues relevant to the recommendation

3.21 The company highlighted that C1-INH treatment is based on human or animal products and may not be acceptable for 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 they noted that Ruconest was not commonly used in clinical practice. The committee noted that some people may refuse human plasma-derived products but understood that the animal-based C1-INH may be used instead. The committee was also aware that oral treatment with attenuated androgens could affect a woman's fertility and is therefore not appropriate for women who could have children. However, the committee noted that C1-INH treatment was available if long-term prevention with oral therapy was contraindicated, for example in pregnant women. It also understood that oral prevention 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 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 document.

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 recurrent attacks of hereditary angioedema and the healthcare professional responsible for their care thinks that lanadelumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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