NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using donidalorsen in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 21 May 2026
- Second evaluation committee meeting: 9 June 2026
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Donidalorsen should not be used for preventing recurrent attacks of hereditary angioedema (HAE) in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with donidalorsen 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 healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, donidalorsen would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether donidalorsen is value for money in this population.

Why the committee made these recommendations

Usual treatment to prevent recurrent attacks of HAE includes berotralstat, C1-esterase inhibitors, garadacimab and lanadelumab.

Evidence from a clinical trial shows that donidalorsen reduces the rate of HAE attacks compared with placebo. It has not been directly compared with any of the usual treatments. An indirect comparison suggests that it is likely to work as well as:

- berotralstat

- C1-esterase inhibitors
- lanadelumab taken every 4 weeks.

But the evidence suggests that donidalorsen may be less effective than garadacimab and fortnightly lanadelumab.

There are uncertainties in the economic model because:

- of how relative treatment effects and long-term attack rates are modelled
- there is no stopping rule included for berotralstat
- subsequent treatments and their impact on costs are not included.

Because of the uncertainties in the clinical- and cost-effectiveness evidence, it is not possible to determine the most likely cost-effectiveness estimates for donidalorsen. So, it should not be used.

2 Information about donidalorsen

Anticipated marketing authorisation indication

2.1 This draft guidance is being issued for consultation before donidalorsen (Dawnzera, Otsuka) has a licence for this indication in the UK. Any recommendations or conclusions in this document are provisional and dependent on the granting of a marketing authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA). The evaluation and consultation processes do not pre-empt, influence or replace the MHRA's independent regulatory assessment. Final guidance will only be published when a marketing authorisation is granted.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for donidalorsen.

Price

2.3 The list price of the 80-mg donidalorsen prefilled pen is currently confidential.

2.4 The company has a commercial arrangement, which would have applied if donidalorsen had been recommended.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Otsuka will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Otsuka, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

Hereditary angioedema

Details of the condition

3.1 Hereditary angioedema (HAE) is a rare genetic condition. It is almost always caused by a mutation affecting the C1-esterase inhibitor (C1-INH) gene, known as type 1 or type 2 HAE. The prevalence of HAE in the UK is at least 1 in 59,000, and about 1,000 to 1,500 people have the condition. It is chronic and involves recurrent unpredictable attacks of swelling in areas of the skin and submucosal tissue. The swelling may happen in the fingers and toes, face, mouth, abdomen, genitalia, gut or airways. It can cause severe pain, and airway swelling (a laryngeal attack) can be life threatening. About 50% of people have an attack before age 10 years and most have their first attack before age 18 years. The patient experts explained that attacks are highly unpredictable and last between 24 and 72 hours. It then takes another 48 to 72 hours to fully recover. After an attack, people can feel drained and have flu-like symptoms and extreme fatigue. The experts also emphasised that every person with HAE is

different and may experience the condition differently. Additional treatment options are important because existing options do not suit everyone with the condition.

The clinical experts explained that attacks should be treated with on-demand treatment as soon they happen. They advised that the aim of preventive treatment is to reduce the number and severity of attacks. The patient and clinical experts emphasised that people with HAE particularly value freedom from attacks. This is because of the severe anxiety caused by anticipating future attacks, which diminishes with increasing time since the last attack. They advised that, although people having existing treatments could have no attacks, breakthrough attacks can occur because HAE is very unpredictable. Clinical experts also discussed how some treatments can lose effectiveness over time (see section 3.2). Attacks are often caused by stressful life events, such as exams, surgery, a car crash, bereavement or giving birth. They may become more pronounced when there are changes in hormone levels, particularly oestrogen, during puberty and menopause. People can also have long periods with more frequent or more severe attacks. This has a significant impact on quality of life and is associated with extreme anxiety. HAE can disrupt education and affect the choice of college, university and career. It can also make travelling for work and leisure extremely challenging. The experts noted the impact in people aged 12 to 17 years, explaining that painful abdominal or facial attacks can lead to stigma and stop people from going out.

The committee recognised that HAE can be severe and debilitating, and that the unpredictability of attacks causes considerable anticipatory anxiety for people with the condition. It understood that the condition varies greatly between different people, so treatment is highly individualised. The committee concluded that there is an unmet need for additional effective treatment options to prevent recurrent attacks of HAE.

Clinical management

Treatment options

3.2 NICE technology appraisals guidance and NHS England clinical commissioning policy outline which treatments can be used to prevent HAE attacks based on eligibility criteria:

- People having 2 or more attacks per week despite oral treatments can have:
  - garadacimab, a monthly subcutaneous injection for people 12 years and over (see NICE's technology appraisal guidance on garadacimab for preventing recurrent attacks of HAE in people 12 years and over; from here, TA1101)
  - lanadelumab, a subcutaneous injection administered every 2 to 4 weeks for people 2 years and over (see NICE's technology appraisal guidance on lanadelumab for preventing recurrent attacks of HAE; from here, TA606)
  - a human-plasma-derived C1-esterase inhibitor administered by slow intravenous injection or infusion every few days or weekly for people of all ages (NHS England clinical commissioning policy on plasma-derived C1-esterase inhibitor for prophylactic treatment of HAE types I and II).
- People having 2 or more attacks per month can have:
  - garadacimab, a monthly subcutaneous injection for people 12 years and over (see TA1101)
  - berotralstat, a daily oral treatment for people 12 years and over (see NICE's technology appraisal guidance on berotralstat for preventing recurrent attacks of HAE; from here, TA738).
- People having fewer than 2 attacks per month can only have on-demand treatment.

The clinical and patient experts explained that the threshold of 2 or more attacks per month for treatment eligibility is arbitrary and creates

unmet need. But they understood that the criteria had been used to enable access for people with a high number of recurrent attacks. Experts also explained that the severity and location of attacks in the body is just as important as the frequency of attacks for treatment decisions. The clinical experts further identified that long-term prophylaxis treatments have about a 70% response rate. People can develop acquired resistance to monoclonal antibodies (such as lanadelumab and garadacimab), meaning that these medicines are no longer effective. So, access to additional treatment options is crucial because of different mechanisms of action. The committee concluded that people with HAE and healthcare professionals would welcome an additional preventive treatment option to improve treatment choice.

Positioning of donidalorsen

3.3 The company identified that the intended positioning of donidalorsen in the treatment pathway for HAE is for preventing recurrent attacks in people 12 years and over who have 2 or more attacks per month. So, the company submission provided results for people who have 2 or more attacks per month and for people who have 2 or more attacks per week (8 or more attacks per month). The company did this to align with the different eligibility criteria for the relevant comparators (see section 3.2). The company's original submission did not include garadacimab as a comparator. It explained that this was because garadacimab was not established clinical practice and had very limited use in the NHS at the time of submission.

The EAG noted that all other relevant comparators had been included in the evaluation appropriately. But it thought that garadacimab should be included in the evaluation because it has positive NICE guidance in the same proposed treatment line and setting as donidalorsen. Before the committee meeting, the company accepted that garadacimab was a relevant decision-making comparator and provided results from a pairwise network meta-analysis (NMA; see section 3.7). The committee concluded

that garadacimab was a relevant comparator and should be included in decision making. It also concluded that the company's overall positioning of donidalorsen and its comparators was appropriate. It further concluded that it would consider cost effectiveness separately in people having 2 or more attacks per week and 2 or more attacks per month.

Clinical effectiveness

OASIS-HAE and OASISplus trials

3.4 The key clinical evidence for donidalorsen came from OASIS-HAE. This was a phase 3, double-blind, randomised, placebo-controlled trial in 91 people aged 12 years and over with type 1 or 2 HAE. It compared donidalorsen 80 mg taken every 4 or 8 weeks with placebo across 3 trial arms. People started treatment once they had had 2 or more attacks during the trial's run-in period. The primary endpoint was the time-normalised number of attacks during the 24-week treatment period. OASISplus was an open-label extension study providing supportive longer-term safety and exploratory effectiveness data. It included a cohort switching from other prophylactic treatments. Both studies were done across multiple international sites, including in the UK. OASIS-HAE was used directly in the company model.

The results from OASIS-HAE showed a least square mean HAE 4-weekly attack rate of 2.26 (95% confidence interval [CI], 1.66 to 3.09) for placebo, 0.44 (95% CI, 0.27 to 0.73) for 4-weekly donidalorsen and 1.02 (95% CI, 0.65 to 1.59) for 8-weekly donidalorsen. This equates to an 81% reduction compared with placebo for 4-weekly donidalorsen and a 55% reduction for 8-weekly donidalorsen. OASISplus showed reductions greater than 90% in the monthly HAE attack rate from baseline in the open-label cohort with donidalorsen. Also, the monthly HAE attack rate for people who switched from other prophylaxis treatments to donidalorsen reduced by 62%. The committee concluded that clinical evidence from OASIS-HAE and

OASISplus suggested that donidalorsen was more effective than placebo at reducing the number of HAE attacks.

Use of other treatments in OASIS-HAE

3.5 In OASIS-HAE, some people had androgens and tranexamic acid alongside trial treatments. The exact numbers are confidential and cannot be reported here. The EAG noted that androgens and tranexamic acid are recognised to reduce HAE attack frequency. Also, androgens are widely used as a long-term prophylaxis treatment for HAE in many countries. For this reason, androgens and tranexamic acid are typically excluded from HAE trials with a defined washout period. A clinical expert consulted by the EAG said inclusion of these treatments in OASIS-HAE may have confounded the treatment effect. The EAG was unable to adjust the trial results to account for androgen and tranexamic acid use because patient-level data was not available. It also noted that this contributed to uncertainty in comparisons to other treatments that did not have androgens and tranexamic acid used alongside them in trials.

Submissions from clinical experts to NICE noted that it was unusual for androgens and tranexamic acid to be used in HAE long-term prophylaxis trials. But they noted that the use of androgens was similar across placebo and 4-weekly donidalorsen arms, so this was not a significant concern. The company explained that it had done an analysis without the data from people who had had androgens and tranexamic acid, and that the results were consistent with and without this data. The committee noted that this analysis had not been provided, and it concluded that it would like to see it.

Baseline characteristics in OASIS-HAE

3.6 The EAG noted that OASIS-HAE had a small number of people in each of the treatment arms, so baseline differences may have had a disproportionate effect on the treatment-effect estimates. The placebo arm included 22 people, the 4-weekly donidalorsen arm included 45 people

and the 8-weekly arm included 23 people. The EAG highlighted the following baseline characteristics of interest in OASIS-HAE:

- Baseline disease burden:
  - Mean run-in attack rates were higher for donidalorsen (4-weekly, 3.61; 8-weekly, 3.18) compared with placebo (2.90).
  - There was a higher mean number of attacks with 4-weekly donidalorsen than with placebo in the 12 months before enrolment.
  - Differences showed that people in the donidalorsen arms entered the trial with a higher disease burden.
  - The effect of differing baseline attack rates between donidalorsen and other treatments is unknown.
- The trial had a limited number of people aged 12 to 17 years, which restricted the conclusions that could be drawn for this age group (0 in the placebo arm, 4 in the 4-weekly donidalorsen arm and 3 in the 8-weekly donidalorsen arm).
- Generalisability to the UK:
  - In the placebo arm, 63.6% were male and 36.4% were female, which the EAG expert highlighted could be unexpected because more females may suffer HAE attacks because of hormonal differences.
  - The trial population mainly consisted of people from a White ethnic background. Most people were recruited from outside the UK.
  - Differences in clinical practice patterns, access to on-demand therapy and patient characteristics may limit the applicability of the results to NHS settings.

    The company explained that the baseline characteristics were broadly well matched across cohorts. Also, it said that some variation was to be expected because of the relatively small sample sizes. It also noted that its clinical experts considered the characteristics of the patient population of OASIS-HAE to be generalisable to people with HAE in the UK. Clinical expert

submissions to NICE noted that OASIS-HAE generally reflects UK clinical practice. Also, the trial was done in UK centres and in line with current clinical practice. But during the committee meeting, clinical experts did note that people recruited to clinical trials might be different to those seen in clinical practice. This is because people whose attacks are well controlled on their current treatment are unlikely to join clinical trials. The committee concluded that OASIS-HAE was generalisable to the UK, although it thought that this was uncertain.

Indirect treatment comparisons

3.7 Key clinical trial evidence for donidalorsen compared it with placebo. It has not been directly compared with other long-term prophylaxis treatments. So, the company did an indirect treatment comparison. This was done using an NMA, anchored using the placebo arms of comparator clinical trials. The trials included:

- OASIS-HAE for 4-weekly and 8-weekly donidalorsen (80 mg)
- HELP for 2-weekly and 4-weekly lanadelumab (300 mg)
- CHANGE for C1-esterase inhibitors
- APeX-2 for berotralstat (150 mg).

The results of the company's NMA are confidential and cannot be reported here. The company noted that the point estimates for donidalorsen were more favourable than for berotralstat, 4-weekly lanadelumab, C1-esterase inhibitors and placebo. But the point estimates were less favourable compared with 2-weekly lanadelumab. The company also noted that credible intervals were wide across all comparators and frequently crossed 1. This showed considerable uncertainty in the relative treatment effects, and no statistically significant differences between treatments were found. The EAG updated the company's NMA to include monthly garadacimab (200 mg), based on the VANGUARD trial. The results are confidential and

cannot be reported here. But the committee recalled the committee's conclusion in TA1101, which was that garadacimab has similar or better clinical effectiveness than berotralstat, C1-esterase inhibitors and lanadelumab.

The company provided a pairwise NMA for donidalorsen compared with garadacimab to support discussions around including garadacimab as a relevant comparator. The results are confidential and cannot be reported here. But the company noted that the point estimates for donidalorsen were less favourable than for garadacimab. The company explained that the results showed no statistically significant difference between donidalorsen and garadacimab. The EAG considered that it would be more useful if the company added garadacimab to its larger NMA, instead of just sharing a pairwise NMA. The committee noted that both the company and the EAG used a random-effects NMA. It asked the company why it opted for a random-effects instead of a fixed-effects NMA, and whether the credible intervals were narrower with a fixed-effects NMA. The company explained that it opted for a random-effects NMA because it could account for heterogeneity across the included trials, unlike a fixed-effects model. It also noted that the point estimates with a fixed-effects model were similar to the random-effects model. The EAG did note that the credible intervals of the point estimates were narrower with the fixed-effects NMA.

The committee concluded that the results of the company's NMA were very uncertain. It thought that a fixed-effects NMA might be more suitable and lead to narrower credible intervals for point estimates, which could reduce uncertainty. It also noted that the NMA only used 1 trial for each comparison. It thought that this meant that the company's measure of between-study heterogeneity was entirely based on the priors used by the company. So, the committee concluded that it would like to see what priors the company had used

for the random-effects NMA. It also requested full results from the fixed-effects NMA (point estimates and credible intervals), including the use of this NMA to estimate cost-effectiveness results. It noted that results should be shown for the random-effects and fixed-effects NMAs and for the steady-state period and full-trial period.

Long-term attack rates

3.8 Data on weekly HAE attack rates was collected for 24 weeks in OASIS-HAE. So, to derive outcomes beyond 25 weeks, the company assumed that an average attack rate would be maintained in the long term. This attack rate was the average rate from the time point at which the treatment reached its maximum effect until the end of the trial. For donidalorsen, this was week 5 in OASIS-HAE based on the steady-state definition. The clinical experts thought that extrapolating the average attack rate from week 5 to week 25 seemed plausible. The EAG noted that the company did not explore alternative approaches such as zero-inflated or Poisson-regression models. These models would account for the high proportion of attack-free periods seen with HAE. The EAG was unable to explore these alternatives because of the lack of individual patient-level data. But it noted that long-term extrapolations in previous NICE technology appraisals materially affected the cost-effectiveness estimates. The committee concluded that the company had not sufficiently explored uncertainty in the long-term attack rates it modelled. It concluded that it would like to see alternative approaches explored, as suggested by the EAG, and verification of the long-term attack rates. It also noted that the long-term attack rate for berotralstat may be overestimated because the company had not implemented the stopping rule (see section 3.11). So, it concluded that it would like to see the long-term attack rate for berotralstat explored, accounting for the stopping rule for people whose condition does not respond.

Economic model

Company's modelling approach

3.9 The company developed a lifetime Markov model to evaluate donidalorsen for people with HAE having 2 or more attacks per month or 2 or more attacks per week. The model used 28-day cycles and included health states for being alive and attack-free, being alive and having an attack, and death. Treatment effects were based on baseline weekly attack rates taken from OASIS-HAE, with no treatment waning applied. The baseline attack rate per week was 0.73 for people having 2 or more attacks per month and 2.00 for people having 2 or more attacks per week. The company's base case was a cost-comparison analysis assuming equal efficacy across long-term prophylactic treatments, so utilities were not included. Published patient and carer utility values from Nordenfelt et al. (2014) were used in a scenario analysis. Costs were sourced from standard NHS and Personal Social Services Research Unit references. The committee concluded that the general model structure was suitable for decision making.

Assuming equal efficacy across treatments

3.10 The company model assumed equal efficacy across all treatments in the model. This meant that the analysis was a cost comparison rather than a cost-utility analysis. The company justified this approach because of the wide and overlapping credible intervals estimated in the NMA results. The point estimates also lacked statistical significance for all comparator treatments (see section 3.7). So, the company thought that it was reasonable to assume similar efficacy and quality-of-life benefits across all treatments. The company also explained that the clinical experts it consulted validated this approach of assuming equal efficacy. The EAG disagreed with the company, outlining that the wide credible intervals showed lack of precision in estimates rather than non-inferiority. It also noted that no margins were prespecified to justify collapsing treatment effects. This meant that interpretation was limited by heterogeneity in

study designs, patient populations and baseline characteristics across trials in indirect comparisons. Also, the EAG noted that the network of evidence was sparse, being anchored only by the placebo arms of each trial. So, the EAG adopted a cost-utility approach in its base case, using the point estimates from its NMA.

One clinical expert submission stated that the outcomes for donidalorsen were broadly consistent with other comparators in the model. The other expert submission stated that donidalorsen was likely to be more effective than berotralstat and lanadelumab, and equally as effective as garadacimab. The committee recalled its earlier conclusion that the results of the company's NMA were very uncertain, and that it would like to see additional analyses (see section 3.7). So, it concluded that the company had not shown that donidalorsen had equal efficacy to the comparators. It also concluded that a cost-utility approach was suitable for decision making.

Berotralstat stopping rule

3.11 TA738 recommends berotralstat as an option for preventing recurrent attacks of HAE. But this is only if it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months (among other criteria). The company's base case did not include this stopping rule in its model. The company explained that including the stopping rule was inconsistent with the equal efficacy assumption across all treatments. It added that including the stopping rule would remove treatment costs for people whose condition does not respond to berotralstat. But it added that it would not recognise the associated poorer health outcomes. So, the company thought that this would bias modelled outcomes in favour of berotralstat.

The EAG explained that the stopping rule for berotralstat has been identified as a key driver of cost effectiveness in previous NICE technology appraisals. So, in the EAG's base case that did not assume

equal treatment effectiveness, the stopping rule was included in the modelling. The company further explained that berotralstat was not the key comparator in this evaluation of donidalorsen. It explained that, given its acceptance of garadacimab as a relevant comparator, the key decision was a cost comparison of donidalorsen compared with garadacimab. So, it said that the berotralstat stopping rule was not relevant. The committee recalled its earlier conclusion that a cost-utility approach is appropriate for decision making. So, it concluded that the stopping rule for berotralstat should be included in the economic model.

Subsequent treatments

3.12 The clinical experts explained that multiple long-term prophylaxis treatments are needed for HAE. This is because some treatments stop working and some are limited by acquired resistance to antibodies (see section 3.2). So, the committee questioned whether the economic model should capture subsequent treatments. It noted that the company's and the EAG's models assumed that people who stop prophylaxis have no further prophylaxis treatment (they just have on-demand treatments). But it noted that patient and clinical experts highlighted the unmet need for additional prophylaxis treatments, especially treatments that are not monoclonal antibodies (like donidalorsen) and so are not at risk of acquired resistance.

The EAG explained that its clinical experts thought that it was appropriate to assume that on-demand treatments are used when prophylaxis treatment is stopped. But it noted that this expert opinion likely reflected historical practice, when prophylaxis treatment options were limited. The EAG acknowledged that this opinion may change with the very recent availability of additional treatment options. The company understood the committee's concern. But it explained that the key decision is a cost comparison of donidalorsen compared with garadacimab when subsequent treatments are not relevant. The committee concluded that subsequent prophylaxis treatments should be included in the modelling in

scenario analyses. It thought that this should be based on expert opinion and available data, and that the clinical outcomes and associated costs of subsequent treatments should be included.

Other modelling assumptions

3.13 The company's base-case model also included key assumptions that the EAG did not raise as key issues. But the committee discussed these assumptions, which included:

- Baseline attack rate: The company's base case assumed the same baseline attack rate for everyone, irrespective of their treatment. This was 0.725 attacks per week for people who had 2 or more attacks per month, based on the placebo arm of OASIS-HAE. For people who had 8 or more attacks per month, 2 attacks per week were assumed based on TA606. The EAG used a pooled baseline attack rate from long-term prophylaxis treatments for the donidalorsen arm in its base case. This was to account for the differences in baseline disease burden in OASIS-HAE (see section 3.6).
- Treatment dosing: The company modelled the proportion of people switching from 2- to 4-weekly lanadelumab dosing as 45% at 12 months. The EAG noted that the clinical experts it consulted suggested that, in practice, switching is variable. So, the EAG included a scenario analysis with 45% switching at 3 months.
- Disutility per administration: The company base case included an annual utility decrement of 0.0003 for intravenous injections and 0.0002 for subcutaneous injections. The EAG considered that disutility should vary with the route and frequency of injections instead of being an annual disutility. But it noted that there was no consensus on the best implementation because disutility over multiple injections is not additive.
- Carer disutility: The company used a carer disutility of 0.0123 for every 0.1 decrement in patient utility was used in its base case. This was the same approach as was used in TA1101.

The committee concluded that the assumptions used by the company for disutility per administration and carer disutility were appropriate for decision making. It also concluded that using the pooled baseline attack rate, as in the EAG's base case, was appropriate. It further concluded that it would like to see further scenario analyses exploring the switching of lanadelumab dosing at 3-, 6-, and 9-month timepoints.

Severity

3.14 NICE's methods for conditions with a high degree of severity did not apply to this evaluation.

Acceptable ICER

3.15 The cost-effectiveness estimates contain confidential prices for treatments, so specific incremental cost-effectiveness ratios (ICERs) cannot be reported here. The company presented their base case using a cost comparison and the EAG presented results from cost-utility analyses. The committee recalled its preference for a cost-utility analysis, and that it had requested additional analyses to support its decision making. It noted that by using cost utility it would need to consider the acceptable ICER for decision making. NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per quality-adjusted life year gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, including on:

- the impact of removing the data from people who had androgens and tranexamic acid in OASIS-HAE
- the generalisability of OASIS-HAE to the UK

- indirect treatment comparisons
- long-term attack rates
- the impact of including subsequent prophylaxis treatments
- varying lanadelumab dose switching.

So, the committee concluded that it was unable to determine an acceptable ICER. But it was able to make the following conclusions about its preferred assumptions:

- using the pooled baseline attack rate from the EAG base case was appropriate
- a cost-utility approach was suitable for decision making
- the stopping rule for berotralstat should be included in modelling.

It also concluded that it would like to see the following additional analysis to support decision making:

- a base-case cost-utility analysis that includes garadacimab as a comparator (see section 3.3)
- an analysis that removes people who had androgens and tranexamic acid in OASIS-HAE (see section 3.5)
- what priors the company used for the random-effects NMA (see section 3.7)
- full results from the fixed-effects NMA (point estimates and credible intervals) including using this NMA to estimate cost-effectiveness results (see section 3.7)
- full results for the random-effects and fixed-effects NMAs and for the steady-state period and full-trial period (see section 3.7)
- an exploration of alternative approaches to modelling long-term attack rates as suggested by the EAG, and verification of the long-term attack rates (see section 3.8)

- an exploration of the long-term attack rate for berotralstat, accounting for the stopping role for people whose condition does not respond (see section 3.8)
- a scenario analysis including subsequent prophylaxis treatments (see section 3.12)
- a scenario analysis including lanadelumab dosing switching at 3, 6 and 9 months (see section 3.13).

Other factors

Equality

3.16 The committee was aware that young people have less access to long-term preventive treatments for recurrent HAE than adults in NHS clinical practice. It noted 2 reasons for this from the access criteria (see section 3.2):

- Age: berotralstat and garadacimab is only available for people 12 years and over.
- Attack frequency (2 or more attacks per month [berotralstat and garadacimab] or 2 or more attacks per week [C1-esterase inhibitors, lanadelumab and garadacimab]): young people tend to have a lower attack frequency than adults, and this may be below the access criteria, but they are significantly affected by the condition.

The committee noted that age is a protected characteristic under the Equality Act 2010. The company confirmed that the anticipated marketing authorisation for donidalorsen is in people 12 years and over, and any recommendation by NICE must be within the marketing authorisation. The company also positioned donidalorsen in people having 2 or more attacks per month. The committee understood that this positioning was consistent with NHS England clinical commissioning policy on plasma-derived C1-esterase inhibitor for prophylactic treatment of HAE types I and II.

The committee also noted that some religious groups may be unwilling to have blood-derived products, such as C1-esterase inhibitors. It noted that religion is a protected characteristic under the Equality Act 2010. It also noted that donidalorsen, garadacimab and lanadelumab are alternatives to C1-esterase inhibitors and are not derived from human plasma. The committee agreed that any recommendation would apply equally to everyone regardless of protected characteristics.

Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of donidalorsen. It noted that the following aspects were raised by the patient and clinical experts:

- Donidalorsen addresses an unmet need for prophylaxis treatments that are not monoclonal antibodies, which are subject to loss of efficacy because of acquired resistance.
- Donidalorsen has quality-of-life impacts related to:
  - attack severity
  - anticipatory anxiety and stress related to future HAE attacks.
- Donidalorsen offers the convenience of an effective treatment that can be self-injected at home.

For these possible uncaptured benefits, the committee concluded that:

- When it determines an acceptable ICER, the committee will take into account the unmet need around treatment options with different mechanisms of action.
- Anticipatory anxiety related to potential future attacks was taken into account in the EAG cost-utility base case by modelling the health-related quality-of-life impacts of both having attacks and being free from attacks.

- The convenience of being able to self-inject donidalorsen at home is similar to that of garadacimab and other treatments.

Overall, the committee concluded that the potential uncaptured benefits did not alter its conclusions on the cost effectiveness of donidalorsen.

Conclusion

Recommendation

3.18 The committee acknowledged that there is an unmet need for different long-term preventive treatments for recurrent attacks of HAE. It concluded that the evidence presented by the company for donidalorsen was uncertain. It also identified additional analyses that it would like to see. This meant that the committee could not determine plausible or acceptable cost-effectiveness estimates. So, donidalorsen should not be used as an option for preventing recurrent attacks of HAE in people 12 years and over.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

Owen Swales

Technical lead

Emily Leckenby

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

ISBN: [to be added at publication]