NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Berotralstat for preventing recurrent attacks of hereditary angioedema

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using berotralstat 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?

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 berotralstat 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: 28 July 2021

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 Berotralstat is not recommended, within its marketing authorisation, for preventing recurrent attacks of hereditary angioedema in people 12 years and older.

1.2 This recommendation is not intended to affect treatment with berotralstat 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 and the young person's parents or carers.

Why the committee made these recommendations

Hereditary angioedema causes severe swelling of various parts of the body. Treatments for preventing recurrent attacks are limited. Berotralstat is an oral treatment used to prevent recurrent attacks.

Clinical trial evidence suggests that berotralstat is effective at reducing the rate of attacks compared with placebo, but by how much is unclear. The evidence is uncertain because the trial:

- was short
- only included a small number of people
- did not adequately measure if berotralstat reduces attack severity, which patients and clinical experts explained is as important as reducing the number of attacks.

Because of the clinical uncertainty the economic model is uncertain too, particularly because of the small number of people in the trial. Also, the model assumes that people would stop treatment with berotralstat if the number of attacks they have does not reduce enough, which might not be appropriate in clinical practice.

Berotralstat does not meet NICE's criteria to be considered a life-extending treatment at the end of life. Also, the most likely cost-effectiveness estimates are higher than what NICE considers a cost-effective use of NHS resources. So berotralstat is not recommended.

2 Information about berotralstat

Marketing authorisation indication

2.1 Berotralstat (Orladeyo, BioCryst) is indicated for 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of berotralstat is £10,205 for a 28-pack of 150 mg capsules (company submission), which equates to an annual cost of £133,120.60. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by BioCryst, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that none of the key issues identified were fully resolved during the technical engagement stage. It recognised that there were areas of uncertainty (issues 1, 2, 3, 4, 5, 6 and 7, see ERG report) associated with the analyses presented and took these into account in its decision making.

It did not discuss issue 4, which was about the uncertainty of the cost-effectiveness estimates from the probabilistic sensitivity analysis. This is because this issue was considered unresolvable. But the committee considered there is no reason to expect that the probabilistic incremental cost effectiveness ratio (ICER) will be substantially higher than the deterministic ICER. It discussed the following issues (issues 1, 2, 3, 5, 6, 7), which were outstanding after the technical engagement stage.

New treatment option

There is an unmet need for effective treatment options for preventing recurrent attacks of hereditary angioedema

3.1 Hereditary angioedema is a rare genetic disorder. It affects approximately 1 per 10,000 to 50,000 people, and usually develops in the first 10 to 20 years of life. It is a relapsing condition that causes unpredictable and recurrent attacks of swelling. This is usually in the mouth, gut or airway, but it can affect multiple places in the body at once. It often leads to difficulty breathing and severe pain. The patient experts explained that acute attacks of hereditary angioedema are difficult to predict and can vary in severity from mild to life threatening. Attacks can significantly affect the quality of life of people with this condition, as well as that of their family members and carers. The patient and clinical experts explained that attacks can be triggered by anxiety and stress; for example, exams, surgery or dental treatment, as well as positive life events such as weddings and holidays. The clinical experts highlighted that usually attacks are treated as they happen. They advised that the aim of prophylactic treatment is to reduce the rate and severity of attacks and allow people to live an attack-free life. There are currently no effective licensed oral prophylactic treatments. Current oral long-term prophylactic treatment includes attenuated androgens, usually danazol. These are prescribed early in the treatment pathway but often have side effects and limited effectiveness. Also, access to androgens is often limited because of supply issues (see section 3.2). The clinical experts explained that

long-term prophylactic treatment with injectable lanadelumab or C1 esterase inhibitors (C1-INH) is only available in England for a very small number of people who have 2 or more clinically significant attacks per week as per NHS England's commissioning policy. The patient and clinical experts also highlighted that there are limited prophylactic treatment options for people with difficult intravenous access and needle phobia. The committee recognised that hereditary angioedema can be a severe and debilitating condition. It acknowledged the lack of effective prophylactic treatment options available to people with this condition. The committee concluded that there is an unmet need for effective treatment options for preventing recurrent attacks of hereditary angioedema.

Treatment pathway and comparators

The company proposes that berotralstat is used after androgens, but this may prevent some people from accessing treatment

3.2 The company positioned berotralstat for people with at least 2 angioedema attacks per month who have used androgens before, or if androgens are unsuitable. To align with its proposed positioning for berotralstat, in the model the company used data on subgroup of patients in APEX-2 who had at least 2 attacks per month and who had used androgens before. This population is narrower than that specified in the marketing authorisation and NICE scope. It is also narrower than the intention to treat population of APEX-2 (n=80 in the intention to treat population compared with n=35 in the company's proposed positioning subgroup), the main source of clinical evidence (see sections 3.4 and 3.5). The intention to treat population in APEX-2 also includes patients who had fewer than 2 attacks per month, and those who had not used androgens before. The clinical experts stated that supply of androgens in the NHS is inconsistent. They explained that access to androgens is variable, is based on local arrangements and people are unable to get them from local pharmacies. One expert highlighted that the Department

of Health and Social Care's advice to clinicians is to not start prescribing androgens to people who have not had them before. The committee further heard that people under 18 cannot have androgens, but people under 18 are included in the marketing authorisation for berotralstat. The committee was concerned that the positioning proposed by the company may inadvertently prevent some people from accessing berotralstat, and that it would consider this in its decision making.

Standard care is an appropriate comparator at the company's proposed positioning of berotralstat

3.3 The company submission compared prophylactic berotralstat with no prophylactic treatment. In both groups, people had standard care for treating attacks when they happen. These treatments include C1-INHs, icatibant and conestat alfa. The ERG noted that this was narrower than the comparators specified in NICE's final scope for this appraisal. However, the ERG's clinical expert agreed with the company's description of how hereditary angioedema is currently treated in the UK. The committee concluded that standard care is an appropriate comparator at the company's proposed positioning of berotralstat.

Clinical effectiveness

The clinical evidence for berotralstat is from APEX-2, a phase 3, randomised, placebo-controlled trial

3.4 The clinical-effectiveness evidence for berotralstat is from APEX-2. This is a 3-part, phase 3, randomised, double-blind, placebo-controlled trial in people 12 years or older with type 1 or type 2 hereditary angioedema. Part 1 of APEX-2 compared berotralstat 150 mg (n=40) with placebo (n=40) over a follow up period of 6 months. People had standard care if they had an attack during the trial period in both the berotralstat and placebo arms (see section 3.3). The placebo arm of APEX-2 informed the clinical evidence for the standard care arm used in the economic model. Berotralstat 110 mg was also included in APEX-2 but was not considered

relevant to this appraisal because this dose will not be licensed or marketed in the UK. The committee was aware of the small sample size of the trial, particularly for the trial data relevant to the company's proposed positioning (see section 3.2). However, it acknowledged that doing a robust trial in hereditary angioedema is difficult because of the rarity of the disease.

Clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known

3.5 Results from APEX-2 show a statistically significant reduction in mean monthly attack rates of 44% with berotralstat compared with placebo. The patient experts explained that a prophylactic treatment that reduces attack rate could potentially be life changing for people with this condition. However, they explained that although the reduction in attack rate is a clinically important outcome for people with hereditary angioedema, the reduction in attack severity would be equally important. They noted that if a treatment did not reduce attack rate, but reduced attack severity, they would still value the option to have that treatment. They further highlighted that the hospitalisation of people with hereditary angioedema is often because of attack severity rather than attack rate. The company and the ERG stated that the location of attack and duration of attack were used as a proxy for attack severity. The company explained that the measure of attack severity in the trial was subjective, so was not considered credible enough to be included as an outcome in the analysis. The committee recognised that it is important to consider evidence on attack severity as well as attack rate when assessing the clinical effectiveness of berotralstat. It concluded that the clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known.

Economic model

The company's model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice

3.6 The company submitted a cohort-level Markov model with 2 health states: alive and dead. The alive health state was split into 2 substates: attack-free or attack. The time spent in each of these substates was determined by treatment-specific attack rates from APEX-2. The model used percentage reductions from baseline attack rates in the berotralstat and placebo arms of APEX-2, applied to the baseline attack rates specified in the model. People in the attack substate incur the costs of an acute attack and lower health benefits compared with those in the attack-free substate. The ERG advised that the model structure is generally acceptable and similar to a previous appraisal in this disease area (see NICE technology appraisal guidance on lanadelumab). In the berotralstat arm of the model, the company applied a treatment continuation rule. This rule states that people can only continue taking berotralstat if they have a reduction in attack rate of at least 50% compared with baseline by 3 months. However, the committee noted that there was no continuation rule in APEX-2 or the marketing authorisation. It was concerned with the choice of a 50% or more reduction in attack rate from baseline as the cut-off point to continue treatment beyond 3 months. The company stated that this 50% or more cut-off point was based on people having 2 or more attacks per month. It noted that applying this cut-off point results in a reduction of 1 whole attack per month. The patient experts explained that if people had fewer attacks but did not reach the threshold of a 50% reduction, they would likely want to continue treatment anyway. Also, even if the number of attacks did not decrease, but the severity did, they would consider it beneficial to continue treatment. The committee noted the importance of the patient experts' comments, and was concerned that it would be difficult to implement the continuation rule in clinical practice. It concluded

that the model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice.

It is appropriate to consider analyses from the subgroup who have used androgens before and the larger subgroup who may have not

3.7 To align with its proposed positioning for berotralstat, the company's model inputs are based on data from subgroup of APEX-2 with a small number of patients (n=35, 17 berotralstat patients and 18 standard of care patients; see section 3.2). The ERG highlighted its concerns with using clinical evidence for attack rate reductions based on a small sample size (n=35). It suggested that analysis using the intention to treat population would provide this evidence for a larger number of people. This would also reduce uncertainty in the cost-effectiveness analysis. In response to technical engagement, the company considered using the intention to treat population from APEX-2 to inform its economic model. But because this included people who would not have berotralstat in UK clinical practice, it suggested that this would undermine the cost-effectiveness evidence used for decision making. Instead, it provided a scenario analysis using clinical evidence from a larger subgroup (n=57) of people with at least 2 attacks per month who may not have previously used androgens. The ERG agreed with using this larger subgroup because it included more patients than the company's proposed positioning subgroup. However, it highlighted that using the larger subgroup will rely on assuming generalisability of relative reductions in attack rate in people who have used androgens before to those who have not. The committee recalled its concerns about the company's positioning (see section 3.2). It concluded that it would consider analyses from the subgroup that has had androgens before as well as the larger subgroup who may not have used androgens before.

It is uncertain how much berotralstat reduces attacks compared with standard care beyond the trial follow up period

3.8 The company's original model used observed data from APEX-2 to inform treatment-specific baseline attack rates. It used the monthly percentage reduction in attack rates from baseline to 12 months for the berotralstat arm, and to 6 months for the standard care arm. To extrapolate the long-term percentage reduction in attack rate in each treatment arm beyond the specified periods, it used the last observed percentage reduction carried forward over the remaining time horizon of the model. The ERG raised several concerns with the company's original base-case analysis:

- It relied on treatment-arm specific baseline attack rates, rather than adjusting these to be equal between arms.
- Percentage reductions in attack rate for people who met the company's criteria to continue treatment at 3 months (see section 3.6; n=8) were calculated from the average baseline attack rate of the wider subgroup (including people who met the criteria and those who did not; n=17), rather than only using the baseline attack rate of people who met the criteria.
- Using the last observation carried forward approach does not recognise the observed variation in monthly attack rates compared with baseline. This may potentially exaggerate the expected difference in attack rate between the berotralstat and standard care arms over the duration of the model (particularly given the small patient numbers).

The company noted the ERG's comments and provided a revised base case, which included:

- a pooled baseline attack rate between the berotralstat and standard care arms
- a separate baseline attack rate for people who met the company's criteria to continue treatment with berotralstat

- an average reduction in attack rate (using data from months 4 to 12) applied from month 12 onwards for the berotralstat arm. This was relative to the baseline attack rate for people who met the criteria to continue treatment with berotralstat.

The committee noted that in its revised base case the company assumed a 0% reduction in attack rate for the standard care arm to be carried forward beyond 6 months in the model. This was different from the ERG's suggested approach to carry forward the average attack rate reduction between months 0 and 6. The ERG explained that the company's approach only removed the placebo effect from the standard care arm. But it suggested that some placebo effect is also likely in the berotralstat arm as well. The committee suggested it may be more appropriate to adjust the average percentage reduction in attack rate in the berotralstat arm carried forward beyond the observed trial period, using the size of placebo effect seen in the standard care arm. It concluded that the revised base case is more robust, but uncertainty remains about the attack rate reduction with berotralstat compared with standard care beyond the trial follow up period.

Treatment-arm specific costs for managing acute attacks taken directly from APEX-2 are appropriate for decision making

3.9 The company's model took treatment-arm specific costs for managing acute attacks from APEX-2. This resulted in the estimated costs per attack being lower in the berotralstat arm than the standard care arm. This was because of a reduced need for multiple administrations of treatments to manage acute attacks. However, the ERG's clinical expert suggested that there was no plausible reason for berotralstat to consistently affect the cost of treating attacks. Because of the small sample size of the company's proposed positioning subgroup (see section 3.2), the ERG advised that it would be more appropriate to use equal acute attack treatment costs between berotralstat and the standard care arms, based on the intention to treat population. In response to technical engagement,

the company highlighted that use of acute treatments in the berotralstat and standard care arms of APEX-2 was consistent between its proposed positioning subgroup, the intention to treat population and the larger subgroup. Clinical advice to the company suggested that a reduced need for multiple treatments for acute attacks in the berotralstat arm was because of reduced attack severity. During technical engagement, the clinical experts highlighted that prophylactic treatment would reduce both the rate and severity of attacks, resulting in lower costs per acute attack overall. They explained that the number of people who need a second dose of treatment to manage acute attacks would reduce if berotralstat reduces attack severity. The committee considered that alternative published data sources may provide information about the use of treatments for acute attacks. However, it concluded that treatment-arm specific costs for managing acute attacks taken directly from APEX-2 were appropriate for decision making.

Health-related quality of life

Additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable

3.10 The company used utility values from Nordenfelt et al. (2014), a Swedish registry study that included EQ-5D-5L values for both the attack-free and attack substates. The ERG highlighted that EQ-5D data was collected in APEX-2. It considered that this should have been explored further, particularly in the APEX-2 intention to treat population given the small sample size of the company's proposed positioning subgroup (see section 3.2) and the continuation rule (see section 3.6). During technical engagement, the company explained that using the EQ-5D data from APEX-2 resulted in implausible utility values for the attack-free health state because they were higher than those of the general UK population. The clinical experts explained that the effect of an attack on quality of life is more likely to be influenced by personal factors and severity of attacks,

rather than prior treatment with androgens or attack rate. They advised that quality of life is better for those in the berotralstat arm compared with the standard care arm when attack free. The ERG also highlighted that the utility values from Nordenfelt et al. were based on a larger sample size and that the attack utility data were collected systematically. In contrast, in APEX-2, the quality of life data collection may not have coincided with an attack. The committee was concerned that using utility values directly from APEX-2 may not adequately capture the effect of attacks on health-related quality of life and do not reflect the effect of attack severity. But it noted that the latter was likely to apply to the utility values from Nordenfelt et al. too. The committee concluded that additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable.

It is not appropriate to include health-related quality of life effects for carers in the base case

3.11 The company's model included a caregiver disutility based on a time trade off study that reflected how anxiety and the need to provide care affect caregivers' health-related quality of life. This was applied in the model for all the time spent caring for a person with an attack in the alive health state. The ERG explained that applying a single carer disutility for every attack and for every person may be too simplistic. It noted that it is unlikely that all attacks will affect carers to the same extent. It also had concerns with how large the carer disutility, but this figure is considered confidential by the company and cannot be reported here. It suggested that this was too large when compared with the range identified in the NICE's decision support unit review of other technology appraisals (0.01 to 0.173 per year). Following technical engagement, the company revised its base case by applying carer disutility to 52% of attacks based on a burden of illness study. The patient experts explained the effect hereditary angioedema attacks have on carers, and the level of anxiety associated with caring for a family member with hereditary angioedema. The

committee heard that, despite a reduction in attack rate, the level of anxiety remains, although often to a lesser extent for both patients and carers. The committee was aware that NICE's guide to the methods of technology appraisal states that the perspective on outcome should be all direct health effects, whether for patients or, when relevant, carers. However, it noted that although many diseases and conditions may adversely affect carers, few technology appraisals model this. For example, carer disutility was not included in a previous appraisal in this disease area (see NICE technology appraisal guidance on lanadelumab). It considered that there was no clear evidence to suggest that the utility gains for carers associated with berotralstat use would be substantially greater than the losses associated with displaced treatments. It concluded that it was not appropriate to include health-related quality of life effects for carers in the base case.

Cost-effectiveness estimates

The cost-effectiveness estimates are highly uncertain, and some are substantially higher than £20,000 per QALY gained

3.12 The committee considered that the company's revised base case following technical engagement was more robust for decision making (see section 3.8). It considered all estimates of cost effectiveness for berotralstat compared with standard care using its preferred assumptions, that is:

- not applying carer disutility to ongoing attacks (see section 3.11)
- treatment-arm specific costs for managing acute attacks taken directly from APEX-2 (see section 3.9).

However, the cost-effectiveness estimates were substantially uncertain because of:

- the uncertainty about the attack rate reduction with berotralstat compared with standard care beyond the trial follow up, a driver of the cost-effectiveness estimate (see section 3.8)
- the small patient numbers from APEX-2 being used to inform the clinical and cost-effectiveness evidence, further exacerbated by the company's proposed positioning subgroup and the continuation rule (see section 3.2)
- the acceptability of the treatment continuation rule in clinical practice (see section 3.6)
- attack severity, a clinically relevant outcome, is not reflected in the utility estimate (see section 3.5).

So the committee considered that that all the cost-effectiveness estimates were highly uncertain. For some clinically plausible scenarios the ICERs were substantially higher than £20,000 per quality-adjusted life year (QALY) gained. So berotralstat cannot be recommended.

End of life

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

3.13 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 berotralstat is a long-term prophylactic treatment and that the company did not make a case for berotralstat to be considered a life-extending treatment. The committee concluded that berotralstat does not meet the criteria to be considered a life-extending treatment at the end of life.

Innovation

Berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema

3.14 The committee considered berotralstat to be innovative because it would be the first licensed oral prophylactic treatment option for people with recurrent attacks of hereditary angioedema. This would mean people would have access to medicine that is more convenient than injectables. The patient and clinical experts explained the importance of reducing attack rate and people being attack free. They highlighted the potential for berotralstat to improve unpredictable and recurrent attacks of swelling and overall quality of life of people with this condition. The committee noted that berotralstat was granted early access to medicines scheme status. This gives people with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation or when there is a clear unmet medical need. The committee concluded that berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema, but all relevant benefits are reflected in the cost-effectiveness estimates.

Equality considerations

There are no equalities issues relevant to the recommendation

3.15 No equalities issues were raised during scoping and technical engagement. The committee considered the implications of the company's positioning for berotralstat (see section 3.2), including any equality considerations. No additional equality issues were raised. The committee concluded that there were no equalities issues relevant to the recommendation.

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. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
July 2021

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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