NICE National Institute for Health and Care Excellence

NICE guidance

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria

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 Pegcetacoplan is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults who have anaemia after at least 3 months of treatment with a C5 inhibitor. It is recommended only if the company provides pegcetacoplan according to the commercial arrangement.

Why the committee made these recommendations

Current treatments for PNH include C5 inhibitors such as eculizumab and ravulizumab. Some people still experience anaemia and symptoms of PNH while having these treatments. Clinical trial evidence suggests that pegcetacoplan improves haemoglobin levels (a measure of anaemia) and haematological symptoms of PNH for people who have anaemia while taking eculizumab. Pegcetacoplan is likely to have the same clinical benefits for people who have anaemia while taking ravulizumab, because ravulizumab is very similar to eculizumab.

For adults with anaemia while having a C5 inhibitor, pegcetacoplan is more effective and costs less than ravulizumab and eculizumab. Therefore, it is recommended.

2 Information about pegcetacoplan

Marketing authorisation indication

2.1 Pegcetacoplan (Aspaveli, Swedish Orphan Biovitrum) is indicated 'in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months'.

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 pegcetacoplan is £3,100.00 for a 1,080-mg vial (excluding VAT; confirmed by company). The company has a commercial arrangement (simple discount patient access scheme). This makes pegcetacoplan 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 Swedish Orphan Biovitrum (Sobi), 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.

New treatment option

People with paroxysmal nocturnal haemoglobinuria would welcome pegcetacoplan as a new treatment option

3.1 Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood condition in which red blood cells are attacked by the body's immune system. The breakdown of red blood cells can happen within the blood vessels (intravascular haemolysis) or outside the blood vessels (extravascular haemolysis). This often results in anaemia, which needs blood transfusions, and severe symptoms of haemolysis. Current treatments for PNH include the C5 complement protein inhibitors eculizumab and ravulizumab. Submissions from the clinical and patient experts advised that people with PNH who are having these treatments often continue to experience anaemia because of extravascular haemolysis. This causes suboptimal disease control and the need for blood transfusions. The committee understood that because pegcetacoplan works by inhibiting the C3 complement protein rather than the C5 complement protein in the immune system, it would likely target both intravascular and extravascular haemolysis. This means it could offer benefits for people who continue to have anaemia while having C5 complement protein inhibitors that only target intravascular haemolysis. Patient expert statements described how current treatments can be inconvenient. This is because of frequent cannulation and because a healthcare professional is needed to administer the treatment by intravenous infusion at a person's home. The committee understood that pegcetacoplan is available as a subcutaneous infusion that can be self-administered and so would offer greater flexibility to people with PNH. The patient expert statements explained that, because pegcetacoplan is

given more frequently than eculizumab and ravulizumab, this could be difficult for some people to manage and may increase the likelihood of injection site reactions. However, they considered these to be minor inconveniences compared with the benefits that pegcetacoplan offers. Patient expert statements also described how treatment with pegcetacoplan has resulted in fewer blood transfusions and improved fatigue levels and quality of life, including a positive effect on their mental wellbeing and ability to work. The committee concluded that people with PNH would welcome pegcetacoplan as a new treatment option.

Treatment pathway

The company's positioning of pegcetacoplan is appropriate

3.2 In England, PNH is managed by the PNH National Service. This consists of 2 centres and 8 outreach clinics, and a local haematologist through a shared care agreement. The severity of symptoms varies between people and over time, which means that not everyone with PNH needs treatment with eculizumab or ravulizumab. The indications for treatment with the current C5 inhibitors are included in the PNH National Service's indications for treatment with eculizumab and NICE's technology appraisal guidance on ravulizumab for treating paroxysmal nocturnal haemoglobinuria. The committee considered that more people are likely to have ravulizumab in the future because of its lower treatment frequency compared with eculizumab. It discussed the company's positioning of pegcetacoplan for adults who have anaemia after at least 3 months of treatment with a C5 inhibitor. It recalled comments from the clinical and patient expert submissions that C5 inhibitors had significantly reduced the disease burden of PNH. However, some people still experience symptoms despite treatment because of extravascular haemolysis. The company's proposed positioning of pegcetacoplan would mean that it would only be offered to people if they still had anaemia after treatment with eculizumab or ravulizumab. The committee noted that the positioning was in line with the marketing authorisation and clinical trial evidence for pegcetacoplan. It was satisfied that this reflected how pegcetacoplan would likely be used in the NHS. Therefore,

it concluded that the company's positioning of pegcetacoplan in the treatment pathway was appropriate.

Clinical evidence

Pegcetacoplan improves change from baseline in haemoglobin level at week 16 compared with eculizumab

3.3 The company submission included the PEGASUS open-label, active-comparator, randomised controlled trial that compared pegcetacoplan with eculizumab in adults who had haemoglobin levels of less than 105 g/litre despite treatment with eculizumab. People were randomised to have either pegcetacoplan or eculizumab. People randomised to the eculizumab arm continued to have it at their current dose that had been stable for at least 3 months before screening. The trial was done in 3 phases:

- 4-week run-in period in which all patients had pegcetacoplan plus eculizumab (baseline was day 28 of the run-in period)
- 16-week randomised controlled period in which patients were randomised to either pegcetacoplan or eculizumab monotherapy
- 32-week open-label period in which all patients who completed the randomised controlled period had pegcetacoplan monotherapy (people who were randomised to have eculizumab completed another 4-week run-in period before switching to pegcetacoplan monotherapy for the remaining 28 weeks).

The primary outcome of the study was the change from baseline in haemoglobin level at week 16, which was statistically significantly higher in the pegcetacoplan arm compared with the eculizumab arm (least squares mean difference 38.4 g/litre, 95% confidence interval [CI] 23.3 to 53.4, $p<0.0001$). The committee concluded that pegcetacoplan improves the change from baseline in haemoglobin level at week 16 compared with eculizumab.

The trial results are generalisable to clinical practice in England

3.4 The PEGASUS trial was done across 44 sites internationally including at a

PNH specialist centre in England. The company considered the generalisability of the trial evidence with an advisory board, including UK clinical experts experienced in the treatment of PNH. The committee acknowledged opinion from both the company's and ERG's clinical experts that the PEGASUS trial results were generalisable to the population who would likely have pegcetacoplan in NHS clinical practice. The committee discussed the company's definition of anaemia in the PEGASUS trial, defined as a haemoglobin level of less than 105 g/litre. It noted comments from the ERG's clinical experts, which suggested that higher haemoglobin levels could also be considered as uncontrolled anaemia in some people with PNH. The company explained that the haemoglobin threshold had been selected based on clinical expert opinion and because it aligned with previous clinical trials in PNH, the published literature and haemoglobin levels observed in PNH registries. It highlighted that based on the literature, the median haemoglobin level of people enrolled in the international PNH Registry was 106 g/litre and in people referred to the UK PNH National Service was 109 g/litre, which are both similar to the threshold used in the PEGASUS trial. The committee considered that although there is some variation in clinical judgement, the company's definition of anaemia would include most people who would be considered to have anaemia after having treatment with eculizumab or ravulizumab in NHS clinical practice. It therefore concluded that the trial results were generalisable to clinical practice in England.

The results of the company's indirect treatment comparison are not robust for decision making

3.5 The company did not identify any direct evidence comparing the clinical effectiveness of pegcetacoplan with ravulizumab. Therefore, it did an anchored matching-adjusted indirect comparison to compare the effectiveness of pegcetacoplan and ravulizumab in people who had previously had eculizumab. The company used individual patient data from the PEGASUS trial for pegcetacoplan and eculizumab and from Study 302 for ravulizumab and eculizumab, which was considered in NICE's technology appraisal guidance on ravulizumab for treating paroxysmal nocturnal haemoglobinuria. The company identified key differences in the designs of the 2 trials that could not be adjusted to

make them comparable. It also identified important differences in the trial eligibility criteria, which meant that it was not possible to accurately match the haemoglobin levels of patients between trials. Both the company and ERG considered that the results of the indirect comparison may be subject to bias because of these differences and because the effect of key effect modifiers (haemoglobin level and history of transfusions) could not be considered in the matching process. The committee concluded that the results of the company's indirect treatment comparison were not robust for decision making.

The company's assumption of equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population is reasonable

3.6 There is no robust evidence comparing the treatment efficacy of pegcetacoplan and ravulizumab (see section 3.5). So, the company assumed equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population (people with anaemia despite treatment with eculizumab). The results from Study 302 showed that ravulizumab was non-inferior to eculizumab, with point estimates favouring ravulizumab for all primary and secondary endpoints, but these differences were not statistically significant. The committee noted that NICE's technology appraisal guidance on ravulizumab for treating paroxysmal nocturnal haemoglobinuria concluded that ravulizumab and eculizumab were similarly effective and had a similar safety profile. The ERG considered that it was not possible to be certain from the available evidence that the efficacy of ravulizumab would be the same as eculizumab in the PEGASUS trial population. This is because of key differences between the PEGASUS trial and Study 302 (see section 3.5). The committee considered that ravulizumab is a re-engineered form of eculizumab and both technologies are biologically very similar with over 99% homology. It noted that the ERG's clinical experts considered that the efficacy of both treatments is likely to be equal in any population. Therefore, the committee concluded that the company's assumption of equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population was reasonable.

Cost effectiveness

The company's model is suitable for decision making

3.7 The company presented a cohort-level state transition model that reflected the evidence available from the PEGASUS trial and included 4 health states:

- no transfusions needed and a haemoglobin level of less than 105 g/litre
- no transfusions needed and a haemoglobin level of 105 g/litre or more
- transfusions needed
- death.

Spontaneous remission was not modelled because the company considered that this would not be expected to vary by treatment. The company's clinical experts considered that extravascular breakthrough haemolysis results in a drop in haemoglobin level and blood transfusions, both of which are captured in the model health states. The model included a 4-week cycle length with half-cycle correction, and outcomes were assessed over a lifetime time horizon. The committee noted that the company's model structure was different to the model presented in NICE's technology appraisal guidance on ravulizumab for treating paroxysmal nocturnal haemoglobinuria, which had 8 states, based on breakthrough haemolysis in addition to a spontaneous remission and death state. It understood that the company considered that the ravulizumab model was not appropriate for capturing the benefits associated with pegcetacoplan, such as preventing extravascular haemolysis or improving fatigue. The committee discussed the company's summary of product characteristics for pegcetacoplan, which indicated that for the first 4 weeks of treatment, pegcetacoplan should be given in addition to a person's current dose of C5 inhibitor treatment. This is to reduce the risk of haemolysis from abruptly stopping treatment with either eculizumab or ravulizumab. It noted that the company's model assumed that there was no overlap of treatments and people started taking pegcetacoplan on its own without a concurrent C5 inhibitor. This was because the company's model had included data from the randomised controlled period, in which patients had either pegcetacoplan or eculizumab, and not the run-in period in which both treatments were given

(see section 3.3). The company explained that, since the trial, it had consulted with clinical experts who considered that such an overlap of treatments would not likely happen in clinical practice. This is because people who switch from eculizumab or ravulizumab to pegcetacoplan will still experience an ongoing effect of C5 inhibition after stopping treatment and so having treatments concurrently is not needed. The committee considered that the company's assumption was reasonable and reflected how pegcetacoplan would likely be used in NHS clinical practice. It noted that the ERG considered that the company's model was well built, and the model structure reflects the PNH treatment pathway with 2 minor exceptions. The ERG considered that the proportion of people having a C5 inhibitor who were having chelation therapies at baseline in the model should be based on the PEGASUS clinical study report rather than the trial run-in period, as used in the company's base case. It also considered that the application of half-cycle corrections should start from cycle 1 rather than cycle 0 as in the company's model, but that implementing this change would have a negligible effect on the cost-effectiveness results. The committee considered the ERG's critique and that the company's model structure was validated by the company's advisory board. It concluded that the company's model was suitable for decision making.

Pegcetacoplan is recommended as a cost-effective use of NHS resources

3.8 The committee considered the ERG's preferred modelling assumptions that included 2 minor revisions to the company's base case:

- using chelation therapy proportions from the PEGASUS clinical study report (see section 3.7)
- including adverse event costs.

Using the confidential discounts for pegcetacoplan and ravulizumab, pegcetacoplan was more effective and less costly compared with both eculizumab and ravulizumab in the company and ERG base cases and in all scenario analyses presented by the company and ERG. Exact results are confidential and cannot be reported here. The committee noted that the total modelled costs were the least expensive for pegcetacoplan, partly because it is self-administered and reduces the need for blood transfusions. The

committee concluded that pegcetacoplan, when compared with eculizumab and ravulizumab, was a cost-effective use of NHS resources. It therefore recommended pegcetacoplan as an option for treating PNH in adults.

Other factors

There are no equality issues relevant to the recommendations

3.9 The committee discussed the potential equality issues raised during scoping. It noted stakeholder comments that pegcetacoplan is given by a subcutaneous infusion and can be self-administered at home. This may have implications for people with physical or learning disabilities, particularly if they have manual dexterity issues. The company explained that if pegcetacoplan was recommended by the committee, it would provide a patient support programme that would identify and support people who may need additional help to take their subcutaneous infusions at home. The committee considered that this would help to reduce inequalities in access to pegcetacoplan treatment because of its method of administration. It noted stakeholder comments that age and pregnancy are protected characteristics and inequalities may arise if different recommendations are made for children and pregnant women. The committee discussed that children and pregnant women were excluded from the PEGASUS trial. It noted a comment from a clinical expert submission that pegcetacoplan should not be used in pregnancy. The committee considered the pegcetacoplan indication is currently limited to adults and it can only recommend a treatment within its marketing authorisation. The committee concluded that there were no equality issues relevant to the recommendations.

The benefits of pegcetacoplan are captured in the cost-effectiveness analysis

3.10 The company considers pegcetacoplan to be innovative because it prevents both intravascular and extravascular haemolysis by targeting the complement cascade earlier than C5 inhibitors. The committee agreed that these are important benefits and recognised that pegcetacoplan will be the first C3 inhibitor licensed for PNH. It recalled

patient expert statements highlighting that treatment with eculizumab and ravulizumab can be inconvenient for some people because of frequent cannulation and because a healthcare professional is needed to administer the intravenous infusion at a person's home. The committee recognised that pegcetacoplan is available as a subcutaneous infusion that can be self-administered and that this may offer benefits for some people compared with current treatments. However, it recalled patient expert statements that because pegcetacoplan is administered more frequently than existing treatments, it may be less convenient for other people. The committee considered that these potential advantages and disadvantages associated with pegcetacoplan's administration may have already been captured in the company's model. This is because the company modelled a disutility for eculizumab to reflect that it has more regular dosing than ravulizumab, and that it is an intravenous infusion whereas pegcetacoplan is a subcutaneous infusion. It assumed no disutility for ravulizumab and pegcetacoplan because they were both assumed to reduce the burden of administration compared with eculizumab. The committee concluded that the benefits of pegcetacoplan are captured in the cost-effectiveness analysis.

4 Implementation

4.1 Section 7 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. Because pegcetacoplan has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after 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 paroxysmal nocturnal haemoglobinuria and the doctor responsible for their care thinks that pegcetacoplan 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.

Anita Sangha
Technical lead

Hannah Nicholas
Technical adviser

Kate Moore
Project manager

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