NCPE Assessment

Technical Summary

Pegcetacoplan (Aspaveli®)

HTA ID: 21064

23 April 2024

Applicant: Swedish Orphan Biovitrum AB

Pegcetacoplan for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in adult patients who are anaemic after treatment with a C5 inhibitor for at least three months.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pegcetacoplan (Aspaveli®).

Following assessment of the Applicant's submission, the NCPE recommends that pegcetacoplan (Aspaveli®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Swedish Orphan Biovitrum AB) Health Technology Assessment of pegcetacoplan (Aspaveli®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In April 2023, Swedish Orphan Biovitrum AB submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pegcetacoplan (Aspaveli®) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in adult patients who are anaemic after treatment with a C5 inhibitor for at least three months. Pegcetacoplan is an inhibitor of the complement proteins C3 and C3b. Pegcetacoplan binds to C3 proteins, inhibiting extravascular haemolysis and the downstream complement cascade that activates C5 proteins, thus inhibiting intravascular haemolysis. Pegcetacoplan is administered at a dose of 1,080mg twice weekly or the dosing frequency can be increased to every three days if lactate dehydrogenase levels are two times the upper limit of normal. As recommended in the Summary of Product Characteristics (SmPC), for the first four weeks of treatment, pegcetacoplan is co-administered with the patient's current dose of C5 inhibitor. Currently, eculizumab is the only C5 inhibitor available in Ireland for the treatment of PNH and is considered to be the main comparator of interest. It is anticipated that eculizumab biosimilar products will become available in the near future. Ravulizumab is a C5 inhibitor that is licensed for the treatment of PNH. However, ravulizumab is currently not reimbursed by the HSE, although it may be reimbursed in the future and is considered informative for decision making. The Applicant estimates that 67% of patients with PNH who are treated with a C5 inhibitor remain anaemic. Swedish Orphan Biovitrum AB is seeking reimbursement of pegcetacoplan on the High Tech Drug Arrangement.

1. Comparative effectiveness of pegcetacoplan

The efficacy and safety of pegcetacoplan was investigated in phase three, randomised, multi-centre, open-label, active-controlled trial, PEGASUS (or APL2-302) where pegcetacoplan was compared with eculizumab. The trial population included adults with PNH who had received treatment with eculizumab at a stable dose for at least three months and had a haemoglobin (Hb) level of 10.5g/dL or less at the screening visit. The trial consisted of a four-week run-in period where all participants received pegcetacoplan at a dose of 1,080mg subcutaneously (SC) twice weekly or every three days, in addition to their current dosage of eculizumab. Following this, participants were randomised to either

continue on pegcetacoplan monotherapy (n=41) or eculizumab monotherapy (n=39) (control arm) for 16 weeks. Subsequently, participants could enter a 32-week open-label extension period where they continued on pegcetacoplan (the control arm received eculizumab in combination with pegcetacoplan for the first four weeks of this period). The primary clinical endpoint was change from baseline (CFB) in Hb level at week 16, excluding data from the four-week run-in period. This endpoint was tested for superiority. Transfusion avoidance was a key secondary endpoint, tested for non-inferiority.

The PEGASUS trial met its primary clinical endpoint with pegcetacoplan demonstrating a least squares mean difference CFB in Hb level of 3.84 g/dL (95% Confidence Interval 2.33 to 5.34), $p<0.0001$. Pegcetacoplan demonstrated non-inferiority to eculizumab with regards transfusion avoidance. The open-label design of the trial is a limitation. The Review Group highlight that the protocol in the control arm (where pegcetacoplan is administered for four weeks before being withdrawn) may have had a destabilising effect on the control arm with regards haematological endpoints. Follow-up data (up to three years) available from an additional open-label extension study indicates maintenance of Hb levels and transfusion avoidance in patients treated with pegcetacoplan. However, the Review Group highlight that comparative efficacy data is only available up to week 16. In the context of a potentially life-long treatment, this leads to uncertainty regarding the sustained benefit of pegcetacoplan relative to eculizumab.

The Applicant conducted a matched-adjusted indirect comparison (MAIC) to obtain relative efficacy estimates for the comparison between pegcetacoplan and ravulizumab. However, due to heterogeneity in trial designs, the trial populations (PEGASUS participants had to have Hb levels <10.5g/dL at baseline) and reduced effective sample sizes for the analysis, the Applicant did not consider the results of the MAIC to be sufficiently robust for decision making. The Review Group note the limitations of the MAIC. Nonetheless, the Review Group requested that the functionality be available in the cost-effectiveness model to input results of the MAIC, for sensitivity analyses. The Applicant did not implement this.

2. Safety of pegcetacoplan

Patients who were randomised in the PEGASUS trial and received at least one dose of monotherapy study drug (n=80) were included in safety analyses. In the pegcetacoplan arm, 34.1% of patients experienced treatment-related adverse events, most of which were

injection site reactions, compared with 17.9% of patients in the eculizumab arm. However, injection site reactions were not considered to be serious or severe and none led to treatment discontinuation. Three patients discontinued pegcetacoplan in the randomised period due to treatment-emergent adverse events, all due to breakthrough haemolysis (BTH) events. No patients discontinued eculizumab due to treatment-emergent adverse events.

3. Cost effectiveness of pegcetacoplan

The cost-effectiveness model uses a cohort-level state transition approach, comprising three health states based on transfusion requirements and Hb level (using a Hb threshold of 10.5g/dL to define anaemia), with an additional health state for death. Patient-level data from the final analysis of the PEGASUS trial (data cut-off date 6 November 2020) are used to inform comparisons between pegcetacoplan and eculizumab. Eculizumab biosimilar products and ravulizumab are both assumed to have equivalent efficacy to eculizumab. The Review Group consider this assumption to be uncertain for ravulizumab, given that the efficacy of ravulizumab has not been ascertained in the population of interest (patients with PNH who have anaemia after treatment with a C5 inhibitor for at least three months).

The Applicant assumed that all patients treated with pegcetacoplan will receive pegcetacoplan twice weekly. The Review Group considered this inappropriate given that a proportion of patients in the PEGASUS trial (about 19.5%) received pegcetacoplan every three days.

The Applicant, based on clinical opinion, assumed that patients treated with pegcetacoplan who experience a BTH event will receive a once-off eculizumab dose of 900mg. BTH events were not explicitly modelled for comparators. The Applicant assumed up-dosing of eculizumab, as permitted in the PEGASUS trial, accounts for BTH management. The Review Group consider eculizumab dosing data available from the HSE to be more appropriate for estimating the cost of eculizumab treatment, as it is reflective of eculizumab dosing in Irish clinical practice.

The Applicant assumes that all patients in the pegcetacoplan arm will achieve a sufficiently high Hb level such that venesections will be the only iron overload treatment required in patients treated with pegcetacoplan. Furthermore, it is assumed that patients treated with pegcetacoplan will require venesections for one year only to manage iron overload. For

comparator arms, it is assumed that iron overload will be managed through administration of iron chelation therapies, continuing over the model time horizon. Costs associated with iron chelation therapies are substantially higher compared with venesections. Additionally, venesections were assumed to be associated with no utility decrement whereas iron chelation therapies were associated with an utility decrement. The Review Group consider there to be a lack of evidence to support these treatment-specific assumptions. Modelling iron overload treatment as a health-state event, dependent on Hb level, would have been more appropriate. Due to this limitation, the Review Group removed costs and disutilities associated with iron overload management in the model, as they imply differential management of iron overload dependent on PNH treatment, as opposed to Hb level, which the Review Group do not deem to be plausible.

The Review Group made a number of changes to obtain the NCPE adjusted base case analysis. The changes that had the greatest effect on cost-effectiveness results include assuming 19.5% of patients on pegcetacoplan will receive it every three days, using HSE data as the source of eculizumab dosing data and removing the disutility associated with intravenous administration (due to a lack of supporting evidence). The Review Group consider cost-effectiveness analyses to be limited due to the methods used to model BTH events and iron overload. Consequently, results of cost-effectiveness analyses are uncertain.

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2.

Table 1: Applicant base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Eculizumab[b]	6,951,552	12.06	-	-	-
Pegcetacoplan[b]	6,901,173	13.85	-50,378	1.79	Pegcetacopan is Dominant[a]
Eculizumab biosimilar[c]	4,277,615	12.06			
Pegcetacoplan[b]	6,901,173	13.85	2,623,559	1.79	1,465,071[a]
Ravulizumab[b]	6,336,027	12.37	-		
Pegcetacoplan[b]	6,901,173	13.85	565,146	1.48	381,790[a]

QALY: quality adjusted life year; **ICER**: incremental cost effectiveness ratio
Note: Figures in the table are rounded, and so calculations may not be directly replicable. Framework Agreement rebate of 8.5% has been applied to pegcetacoplan, eculizumab (originator) and ravulizumab. Discount rate of 4% is applied to costs and outcomes.
[a] Corresponding probabilistic ICERs using 1,000 iterations: vs eculizumab (originator)= Dominant; vs eculizumab biosimilar=€1,458,003

/QALY; vs ravulizumab=.€380,454/QALY

[b] A PAS is in place for eculizumab, not considered in this table. Ravulizumab is not currently reimbursed by the HSE. There is a PAS offer for pegcetacoplan included as part of this submission, not considered in this table

[c] It is assumed that the eculizumab biosimilar has a price equivalent to 55% of the price-to-wholesaler of the originator (Soliris®), in line with the Medicines for Ireland Agreement 2021. However, hospitals may be able to negotiate contract prices that are considerably less expensive than this.

Table 2: NCPE adjusted base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Eculizumab[a,b] (originator)	6,566,225	12.41	-	-	-
Pegcetacoplan[a,b]	7,278,977	13.85	712,752	1.43	497,004
Eculizumab[a,b,c] (biosimilar)	4,016,259	12.41	-	-	-
Pegcetacoplan[a,b]	7,090,538	13.85	12.41	1.43	2,143,704
Ravulizumab[a,b]	6,166,126	12.42	-	-	-
Pegcetacoplan[a,b]	7,090,538	13.85	924,412	1.43	647,536

QALY: quality adjusted life year; **ICER**: incremental cost-effectiveness ratio

NOTE: Figures in the table are rounded, and so calculations may not be directly replicable. Framework Agreement rebate of 8.5% has been applied to pegcetacoplan, eculizumab (originator) and ravulizumab. Discount rate of 4% is applied to costs and outcomes.

[a] Corresponding probabilistic ICERs using 1,000 iterations: vs eculizumab (originator) = €483,815/QALY; vs eculizumab biosimilar =€2,135,724/QALY; vs ravulizumab = €641,425/QALY.

[b] A PAS is in place for eculizumab, not considered in this table. Ravulizumab is not currently reimbursed by the HSE. There is a PAS offer for pegcetacoplan included as part of this submission, not considered in this table.

[c] It is assumed that the eculizumab biosimilar has a maximum supplier proposed price equivalent to 55% of the price-to-wholesaler (PTW) of the originator (Soliris®), in line with the Medicines for Ireland Agreement 2021. However, hospitals may be able to negotiate contract prices that are considerably less expensive than this.

For the comparison with eculizumab, in the Applicant base case, the probability of pegcetacoplan being cost-effective was 75% and 87% at the willingness-to-pay (WTP) thresholds of €20,000/QALY and €45,000/QALY, respectively. In the NCPE adjusted base case, the probability of pegcetacoplan being cost-effective, compared with eculizumab, was 0.1% and 0.2% at the WTP thresholds of €20,000/QALY and €45,000/QALY, respectively. In both the Applicant base case and NCPE adjusted base case analyses, the probability of pegcetacoplan being cost-effective, compared with eculizumab biosimilar and ravulizumab respectively, was 0% at both WTP thresholds. Table 3 outlines the total rebate on the price-to-wholesaler of pegcetacoplan that would be required to achieve cost-effectiveness at both WTP thresholds, based on the NCPE adjusted base case.

Table 3 Total rebate on the price-to-whoelsaler of pegcetacoplan required to achieve cost-effectiiveness

	Pegcetacoplan vs eculizumab	Pegcetacoplan vs eculizumab biosimilar	Pegcetacoplan vs ravulizumab
ICER		**% reduction in pegcetacoplan PtW**	
€45,000/QALY	18%	52.7%	21.12%

€20,000/QALY	18.5%	53.2%	21.64%

QALY: quality adjusted life year; **ICER**: incremental cost-effectiveness ratio; PtW: price to wholsesaler
It is assumed that the eculizumab biosimilar has a price equivalent to 55% of the price-to-wholesaler of the originator (Soliris®), in line with the Medicines for Ireland Agreement 2021.

The basecase assumes that eculizumab biosimilar products are priced at 55% of the price-to-wholesaler of the originator. The Review Group conducted a scenario analysis where the price is estimated to be 25% of the price-to-wholesaler. Using the NCPE adjusted base case, this increases the ICER for the comparison with eculizumab biosimilar to €3,506,159/QALY.

4. Budget impact of pegcetacoplan

The price-to-wholesaler of one 20mL vial containing 1,080mg of pegcetacoplan is €3,672. The Applicant assumed that pegcetacoplan will be administered twice weekly and there will be no co-administration with eculizumab for the first four weeks of pegcetacoplan therapy, resulting in an annual, per-patient, course cost of €477,215, including VAT. The Review Group assumed that 19.5% of patients will receive pegcetacoplan every three days and eculizumab will be co-administered with pegcetacoplan for the first four weeks of treatment, in accordance with the SmPC recommendation. The per-patient cost of pegcetacoplan in year one is estimated to be €525,973 (including VAT) when co-administered with eculizumab and €512,359 (including VAT) when co-administered with eculizumab biosimilar. From year two onwards, the Review Group estimate the annual per-patient treatment course cost of pegcetacoplan to be €492,700, including VAT.

Many of the budget impact inputs are uncertain and there is, therefore, considerable uncertainty associated with budget impact estimates. The Applicant estimated that three patients would be treated with pegcetacoplan in year one, rising to eight patients in year five. The Applicant estimated that the five-year gross drug budget impact of pegcetacoplan is €12.15 million including VAT. The five-year net drug budget impact of pegcetacoplan is estimated to be €2.95 million, including VAT. The Review Group, instead used assumptions, regarding pegcetacoplan and eculizumab dosing, that are informed by Irish clinical practice. The Review Group estimate the five-year gross drug budget impact of pegcetacoplan to be €13.45 million including VAT and the five-year net drug budget impact to be €4.42 million including VAT.

5. Patient Organisation Submission

A patient organisation submission was received from PNH Support.

6. Conclusion

The NCPE recommends that pegcetacoplan not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.