ASSESSMENT OF INNOVATIVENESS

CTS February 2022

Medicine: ASPAVELI® (pegcetacoplan)

Indication: ASPAVELI® is indicated in the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who remain anemic after treatment with a C5 inhibitor for at least 3 months.

THERAPEUTIC NEED		
MAXIMUM	Absence of therapeutic options for the specific indication.	THE
IMPORTANT	Presence of therapeutic alternatives for the specific indication, but not produce an impact on clinically relevant and validated outcomes for the pathology in question.	
MODERATE	Presence of therapeutic alternatives for the specific indication with an impact that can be assessed as limited on outcomes recognized as clinically relevant and/or with a uncertain or not entirely satisfactory safety profile.	X
RARE	Presence of one or more therapeutic alternatives for the specific indication with evaluable impact as high on outcomes recognized as clinically relevant e with a favorable safety profile.	THE
ABSENT	Presence of therapeutic alternatives for the specific indication capable of modify the natural history of the disease and with a favorable safety profile.	THE

Comment:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematological disorder caused by a clonal disorder of haematopoietic stem cells, with the production of mature cells (erythrocytes, white blood cells and platelets) which have characteristic membrane defects.

PNH manifests clinically as chronic hemolysis with acute complement-mediated episodes, which can lead to debilitating and potentially fatal complications, including anemia, dyspnea, fatigue, smooth muscle dystonia, renal failure, and venous thrombosis. PNH is also associated with variable bone marrow failure, such as aplastic anemia (AA) or myelodysplastic syndrome (MDS), further worsening the clinical picture.

To effectively counteract PNH, both intravascular hemolysis and extravascular hemolysis must be controlled. The C5 protein inhibitors, the current standard of care, only counteract intravascular hemolysis, resulting in suboptimal disease control and remaining symptoms, which may influence the course of the disease and the function of the bone marrow [1] [2] [3] [4]. The blockade of the complementary cascade at the C5 level in fact determines an accumulation of C3 on the erythrocytes, which are then phagocytosed in the liver/spleen, leading to the development of extravascular hemolysis. The simple inhibition of membrane attack complex (MAC) formation by eculizumab is therefore insufficient to fully control the development of the disease. More than half of the cases treated with eculizumab benefit only from a reduction in the frequency of transfusions, and in a third of patients the transfusion requirements and symptoms remain unchanged [6]. A real-life study has shown that up to 89% of patients treated with a complement protein C5 inhibitor for 18 months do not have a complete response (no need for transfusion, hemoglobin level in range and stable, no evidence of hemolysis) and 40% remained anemic [5].

Therefore, complement C5 protein inhibitors (eculizumab and ravulizumab) are accompanied by a high need clinical dissatisfied since they do not act in any way on extravascular hemolysis and that in many patients do not allow normalization of hemoglobin levels [1]. In many patients treated with inhibitors of

C5 protein, although LDH levels are well controlled, reticulocyte and bilirubin levels remain elevated, indicating hemolysis in course.

The PNH Education Study Group (PESG) groups treatments for patients with PNH into three categories: therapies support/immunosuppressives (transfusion, folic acid supplement, iron and vitamin B12, corticosteroids, treatment with anticoagulants), therapies that modify the course of the disease (eculizumab, meningococcal prophylaxis) and potential curative treatments (allogeneic stem cell transplant).

Guidelines for the diagnosis, treatment and management of PNH have been described by several organizations dealing with the disease. The main ones are those outlined by the International PNH Interest Group (I-PIG) in 2016 and by PNH Education Study Group (PESG) in 2016.

The International PNH Interest Group (I-PIG) guidelines correlate patient classification with available therapeutic options. The subdivision of patients into treatment classes is made on the basis of flow cytometry, reticulocyte count, serum LDH concentration and bone marrow evaluation. Patients with subclinical PNH do not require specific treatments, but to define and treat the underlying bone marrow failure. Treatment with eculizumab may be useful in patients with PNH associated with marrow aplasia or myelodysplasia in the presence of a large PNH clone. Finally, the

treatment is recommended in classic PNH

In consideration of the approved clinical indication of pegcetacoplan, which is placed in second line compared to protein inhibitors C5, alternatives available for patients with PNH who have an inadequate response to treatment with a C5 inhibitor should be considered. In this class of patients, in the case of an inadequate response to treatment, the I-PIG guidelines recommend increasing the dose of eculizumab, bone marrow transplant, splenectomy or supportive therapies such as transfusions and corticosteroids.

Allogeneic haematopoietic stem cell transplantation, although it can be considered a curative treatment, is generally limited to the most severe forms of PNH due to the high risks of treatment.

In conclusion, there are therapeutic alternatives for the specific indication, considered by the guidelines as supportive therapies, which however, in the population subject to the indication, produce a limited impact on clinically relevant outcomes for the pathology, so much so that patients are still anemic despite the use of a C5 inhibitor and supportive therapy. There is also the possibility of resorting to marrow transplant for patients with particularly severe disease, but with no safety profile satisfying. For this reason, the therapeutic need can be considered MODERATE.

References:

[1] Risitano AM, Marotta S, Ricci P, Marano L, Frieri C, Cacace F, Sica M, Kulasekararaj A, Calado RT, Scheinberg P, Notaro R, Peffault de Latour R, «Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position PaperFrom the SAAWP of the EBMT,» Front Immunol, 2019 Jun 14;10:1157.

[2] Brodsky RA, «Paroxysmal nocturnal hemoglobinuria,» Blood, 2014 Oct 30;124(18):2804-11.

Risitano AM, Notaro R, Luzzatto L, Hill A, Kelly R; Hillmen P, «Paroxysmal nocturnal hemoglobinuria-hemolysis [3] before and aftereculizumab,» N Engl J Med, 2010; 363 (23): 2270-2.

Brodsky RA, Peffault de Latour R, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, Hillmen P, Maciejewski JP, Szer J, [4] Lee JW, Kulasekararaj AG, Volles L, Damokosh AI, Ortiz S, Shafner L, Liu P, Hill A, Schrezenmeier H, «Characterization of breakthrough hemolysis eventsobserved in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria,» Haematologica, 2021 Jan 1;106(1):230-237.

[5] Debureaux PE, Cacace F, Silva BGP, Barone F, Calado R, Sicre de Fontbrune S, Soret-Dulphy J, Ricci P, Sica M, Notaro R, Scheinberg P,Kulasekararaj A, Risitano AM, de Latour RP, Frieri C, «Hematological Response to Eculizumab in Paroxysmal Nocturnal Hemoglobinuria: Application of a Novel Classification to Identify Unmet Clinical Need and Future Clinical Goals,» Blood, 2019; 134 (1): 3517.

[6] DeZern AE, Dorr D, Brodsky RA, «Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria,» Eur J Haematol, 2013 Jan;90(1):16-24.

ADDED THERAPEUTIC VALUE		
MAXIMUM	Greater efficacy demonstrated on clinically relevant outcomes compared to therapeutic alternatives (if available). The drug is able to cure the disease or however, to significantly modify its natural history.	THE
IMPORTANT	Greater demonstrated efficacy on clinically relevant outcomes, or ability to reduce the risk of disabling or potentially fatal complications, or better risk/benefit ratio (R/B) compared to alternatives, or ability to avoid the use of high-risk clinical procedures. The drug modifies the natural history of the disease in a subpopulation of patients, or in any case represents a clinically relevant advantage, for example in terms of quality of life and interval free from the disease, compared to available therapeutic alternatives.	THE
MODERATE	Moderate or demonstrated increased efficacy in certain patient subpopulations or outcomes surrogates, and with limited effects on quality of life. For conditions in which the absence of a comparator is admissible, availability of suggestive evidence of better clinical efficacy and profile R/B more favorable than to available therapeutic alternatives.	X
RARE	Greater efficacy which, however, has been demonstrated on outcomes that are not clinically relevant or appears to be small extent. Minor benefits (e.g. via di more favorable administration) compared to available therapeutic alternatives.	THE
ABSENT	Absence of additional clinical benefit compared to therapeutic alternatives available.	THE

Comment:

To effectively counteract PNH, both intravascular hemolysis and extravascular hemolysis must be controlled. The C5 protein inhibitors, the current standard of care, only counteract intravascular hemolysis, resulting in suboptimal disease control and remaining symptoms, which may influence the course of the disease and the function of the bone marrow.

Furthermore, the currently available C5 inhibitors, eculizumab and ravulizumab, are both administered intravenously, resulting in a high organisational, economic and social impact for the structures and for patients/caregivers.

Pegcetacoplan exerts inhibition at the C3 level, allowing to control hemolysis both at the intravascular and extravascular. Data from the pivotal study demonstrated a superiority of pegcetacoplan over eculizumab in terms of efficacy on the primary endpoint (change in hemoglobin value compared to baseline). In particular, hemoglobin levels, compared to the group treated with eculizumab, increased on average by 3.84 g/dL and these values remained stable for up to 48 weeks; the percentage of patients who did not require transfusions was 85.4% in the group treated with Aspaveli, compared to 15.4% of patients in the group treated with eculizumab. The drug also demonstrated non-inferiority compared to eculizumab for all key secondary endpoints, including transfusion requirement except for the change from baseline endpoint of LDH, for which the values still indicate an advantage of pegcetacoplan compared to eculizumab.

Overall, the safety profile of pegcetacoplan does not appear to differ significantly from that of eculizumab, although the available data concern a limited patient population and for a limited follow-up period.

In conclusion, pegcetacoplan showed superiority over available therapeutic alternatives (C5 inhibitors) on surrogate endpoints, configuring a MODERATE added therapeutic value.

QUALITY OF TESTS

(See attached GRADE pro table):

HIGH		x
MODERATE		THE
LOW		THE
VERY LOW		THE

Comment:

Based on the considerations made through the Grade method (see attached table), the main phase 3 clinical study *APL2-302* is a randomized, prospective, multicenter, open-label, control arm with active comparator, which is attributed a high quality of tests.

OVERALL JUDGMENT ON INNOVATIVENESS

In consideration of: 1) MODERATE therapeutic need 2) MODERATE added therapeutic value 3) HIGH quality of evidence, the innovativeness conditioned on ASPAVELI® in the requested indication can be recognized.

Author(s):

Question: Pegcetacoplan versus eculizumab for paroxysmal nocturnal hemoglobinuria (PNH)

Setting: Patients with anemia after at least 3 months of treatment with a C5 inhibitor

Bibliography: Hillmen P, Szer J, Weitz I, Röth A, Höchsmann B, Panse J, Usuki K, Griffin M, Kiladjian JJ, de Castro C, Nishimori H, Tan L, Hamdani M, Deschatelets P, Francois C, Grossi F , Ajayi T, Risitano A, Peffault de la Tour R. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2021 Mar 18;384(11):1028-1037. doi: 10.1056/NEJMoa2029073. PMID: 33730455.

ÿ of studies	Study design	Certainty assessment: Risk of distortion	Certainty assessment: Lack of reproducibility of results	Certainty assessment: Lack of generalizability to	Certainty assessment: Imprecise it is	Certainty assessment: Further considerations pegcetacopl an	ÿ of patients: eculizumab	Effect the: Relative o(95% THERE)	Effect the: Absolutely o(95% THERE)	Right	Importance
Change in hemoglobin level at week 16 (during the randomized control period) from baseline (follow up: 60 weeks; assessed by: g/dL least square mean (SE))											
1	randomized studies	non important	non important	non important	non important	no the	41	39	·	mean **3.84 g/dL greater** (2.33 greater a 5.34 greater)	ÿÿÿÿ High	CRITIC
No need for transfusions at week 16 (follow up: 60 weeks; assessed with: %)											
1	studies randomized	non important	non important	non important	non important	no the	35/41 (85.4%)	6/39 (15.4%)	**RR 5.55** (2.63 a 11.71)	**70 plus per** 100 (from 25 plus to 100 plus)	ÿÿÿÿ High	IMPORTANT
Change in reticulocytes at week 16 compared to baseline (follow up: 60 weeks; assessed with: 10^9/L Least Square Mean (SE))											
1	studies randomized	non important	non important	non important	non important	no the	41	39	·	mean **163.61 10^9/ L lower** (189.91 less than 137.3 inferior)	ÿÿÿÿ High	IMPORTANT
Change in LDH at week 16 from baseline (follow up: 60 weeks; assessed by: U/L Least Square Mean (SE))											

Author(s):

1	studies randomized	non important	non important	non important	non important	no the	41	39	.	mean **4.63** **Lower U/L** (181.3 lower a 172.04 greater)	ÿÿÿÿ High	IMPORTANT

Change in FACIT-Fatigue score at week 16 compared to baseline (follow up: 60 weeks; assessed by: Least Square Mean (SE))

1	studies randomized	non important	non important	non important	non important	no the	41	39	.	mean **11.87** **greater** (5.49 greater at 18.25 greater)	ÿÿÿÿ High	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio