Report Ultomiris®-Ravulizumab

Product & Mechanism of action

Substance: Ravulizumab

Brand Name: Ultomiris

Originator/licensee: Alexion AstraZeneca Rare Disease

Classification: NI

ATC code: L04AA43

Orphan Status:
Eu: No
Us: Yes

Mechanism of action:
Ravulizumab specifically binds to human complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b (the initiating subunit of the terminal complement complex [C5b-9]) during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming membrane attack complex C5b-9 while preserving the proximal or early components of complement activation (C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes. [1]

Authorized indications Licensing status

Authorized Indication:
EMA: Ravulizumab is indicated in the treatment of paediatric pts with a body weight of 10 kg or above with PNH:
-in pts with haemolysis with clinical symptom(s) indicative of high disease activity.
-in pts who are clinically stable after having been treated with eculizumab for at least the past six months. [2]

Route of administration: IV

Licensing status
EU CHMP P.O. date: 22/07/2021
FDA M.A. date: 07/06/2021

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: No

ABBREVIATIONS:
AE: Adverse event
CHMP: Committee for Medicinal Products for Human Use
EU: European Union
IV: intravenous
LDH: lactate dehydrogenase
M.A.: Marketing Authorization
P.O.: Positive Opinion
PNH: Paroxysmal Nocturnal Haemoglobinuria
Pts: patients
Q4w: once every 4 weeks
Q8w: once every 8 weeks
TA: transfusion avoidance
ULN: Upper Limit of Normal
ws: weeks

Essential therapeutic features

Summary of clinical EFFICACY: NCT03406507, EudraCT 2017-002820-26, ALXN1210-PNH-304: is a phase 3, multi-center, single arm, open-label study, in eculizumab-experienced and complement inhibitor treatment-naïve pediatric patients with PNH. Pts<18 years and weighing ≥5 kg, with diagnosis of PNH and presence of one or more of the following PNH-related signs or symptoms within three months of screening: LDH level ≥1.5×ULN for pts not being treated with eculizumab at screening and LDH level ≤1.5×ULN for pts taking eculizumab. Pts received a loading dose of ravulizumab, followed by maintenance treatment dose on day 15 and subsequent treatments q8w thereafter for pts weighing ≥20kg, or q4w for pts weighing <20kg. A total of 13 pediatric pts (9-17 years old; 5 naïve, and 8 eculizumab experienced) treated with Ravulizumab, were followed for 26 ws. Primary outcomes were pharmacokinetic (Maximum and Trough serum concentration) and pharmacodynamic parameters (free C5 concentrations). [3,4] Complete inhibition of serum free C5 was observed by the end of the first infusion and sustained throughout the entire 26-w treatment period in both adult and pediatric pts with PNH.

Summary of clinical EFFICACY:

		ALXN1210-PNH-304			
		N	**C5 Inibitor-Naïve**	**N**	**Eculizumab treated**
Cmax (mcg/mL)	**Loading Dose**	4	733 (14.5)	8	885 (19.3)
	Mantein. Dose	4	1490 (26.7)	8	1705 (9.7)
Ctrough (mcg/mL)	**Loading Dose**	4	368 (14.7)	8	452 (15.1)
	Mantein. Dose	4	495 (21.3)	8	566 (12.2)

Summary of clinical SAFETY: The most common AEs among pediatric pts treated with ravulizumab are summaries below. [3,4]

AE	**Treatment Naïve (N=5)**	**Eculizumab Experienced (N=8)**	**Total**
Anemia	1 (20%)	2 (25%)	3 (23%)
Abdominal pain	0	3 (38%)	3 (23%)
Constipation	0	2 (25%)	2 (15%)
Pyrexia	1 (20%)	1 (13%)	2 (15%)
Upper Respiratory tract infection	1 (20%)	6 (75%)	7 (54%)
Pain in extremity	0	2 (25%)	2 (15%)
Headache	1 (20%)	2 (25%)	3 (23%)

Ongoing studies:
- ***For the same indication:*** *Estimated study (*NCT03406507*) completion in June2025.*
- ***For other indications:*** *Yes*

Discontinued studies (for the same indication): No

References:

1.https://go.drugbank.com/drugs/DB11580 (last accessed on 10 August 2021);
2.https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ultomiris-1 (last accessed on 10 August 2021);
3.https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761108s012lbl.pdf (last accessed on 23 August 2021);
4.https://www.io.nihr.ac.uk/wp-content/uploads/2021/01/28894-TSID_10514-Ravulizumab-for-Paroxysmal-Nocturnal-Haemoglobinuria-V1.0-JAN2021-NON-CONF.pdf (last accessed on 23 August 2021);
5.Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. [Updated 2021 Apr 7]. https://www.ncbi.nlm.nih.gov/books/NBK562292/
6.https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/17/1873-public-summary-opinion-orphan-designation-polyoxy-12-ethanediylalpha-hydro-omega-hydroxy-1515_en.pdf (last accessed on 10 August 2021);
7.https://www.osservatoriomalattierare.it/malattie-rare/emoglobinuria-parossistica-notturna/14892-emoglobinuria-parossistica-notturna-pazienti-medici-e-ricercatori-in-campo-per-il-patient-s-day (last accessed on 10 August 2021);
8.Sahin F, Akay OM, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. American journal of blood research. 2016;6(2):19;
9.https://clinicaltrials.gov/ct2/results?intr=Ravulizumab&recrs=b&recrs=a&recrs=f&recrs=d&recrs=h&recrs=e&recrs=m&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply (last accessed on 10 August 2021);
10.https://adisinsight.springer.com/drugs/800042001 (last accessed on 25 August 2021);
11.https://clinicaltrials.gov/ct2/results?cond=Paroxysmal+Nocturnal+Haemoglobinuria&recrs=b&recrs=a&recrs=f&recrs=d&recrs=h&recrs=e&recrs=m&age_v=&age=0&gndr=&type=&rslt=&phase=2&Search=Apply (last accessed on 10 August 2021).

NHS impact

Cost of therapy:
In Italy, IV Ravulizumab (30 ml 10 mg/ml; for adult indication) costs 8,282.01€*(ex-factory price 5,018.18€).
**Retail price including VAT*

Epidemiology:
PNH is rare, with occurrence estimated as high as 15.9/1 Mil. individuals worldwide [5]. In 2017, PNH affected less than 0.1/10,000 people in the EU [6]. In Italy, there are at least 250 affected people (within June 2019) [4,7].

POSSIBLE PLACE IN THERAPY
Ravulizumab is as effective and costs less than eculizumab and will provide a 1st-line treatment option for paediatric patients with PNH.
Currently, allogeneic bone marrow transplantation is the only potential curative treatment for PNH selected pts [4,8].

OTHER INDICATIONS IN DEVELOPMENT
Neuromyelitis Optica; Amyotrophic Lateral Sclerosis; Thrombotic Microangiopathy; Myasthenia Gravis, IgA Nephropathy, COVID-19 Severe Pneumonia; Acute Lung Injury; Acute Respiratory Distress Syndrome; Viral Pneumonia; Acute Kidney Injury. [9,10]

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Crovalimab [11]

*Service reorganization: No
*Possible off label use: Yes

Issued on: