11 June 2019
EMADOC-2005359794-76678
EMA/OD/0000004229
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Ultomiris (ravulizumab)
Treatment of paroxysmal nocturnal haemoglobinuria
EU/3/16/1661
Sponsor: Alexion Europe SAS

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Active substance	Fc- and CDR-modified humanised monoclonal antibody against C5
International Non-Proprietary Name	Ravulizumab
Orphan indication	Treatment of paroxysmal nocturnal haemoglobinuria
Pharmaceutical form	Concentrate for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L04AA
Sponsor's details:	Alexion Europe SAS 1-15 avenue Edouard Belin 92500 Rueil-Malmaison France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alexion Europe SAS
COMP opinion date	21 April 2016
EC decision date	30 May 2016
EC registration number	EU/3/16/1661
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	J. Camarero Jiménez, A. Gyurasics
Applicant	Alexion Europe SAS
Application submission date	27 June 2018
Procedure start date	19 July 2018
Procedure number	EMA/H/C/0004954
Invented name	Ultomiris
Therapeutic indication	Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH): • in patients with haemolysis with clinical symptom(s) indicative of high disease activity • in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months Further information on Ultomiris can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/ultomiris
CHMP opinion date	26 April 2019
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	M. Mozina, A. Magrelli
Sponsor's report submission date	1 February 2019
COMP discussion and adoption of list of questions	15-17 April 2019
Sponsor's removal request	8 May 2019
Removal from the Community Register	11 June 2019

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing Fc- and CDR-modified humanised monoclonal antibody against C5 was considered justified based on preliminary clinical data supporting reduction of haemolysis in treated patients affected by the condition;
- the condition is life-threatening and chronically debilitating due to the complications of the chronic haemolysis such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs;
- the condition was estimated to be affecting less than 0.2 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Fc- and CDR-modified humanised monoclonal antibody against C5 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support improved reduction of haemolysis compared to the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Paroxysmal nocturnal haemoglobinuria is a clonal, hematopoietic stem cell disorder. It manifests with a chronic haemolytic anaemia from uncontrolled complement activation, a propensity for thrombosis and marrow failure. The haemolysis is largely mediated by the alternative pathway of complement and clinical manifestations have been linked to the deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs). In particular, patients' erythrocytes become highly vulnerable to complement-mediated lysis owing to a reduction, or absence, of the complement regulatory proteins CD55 and CD59 (DeZem and Brodsky Hematol Oncol Clin North Am. 2015 Jun;29(3):479-94).

The proposed therapeutic indication "indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria" falls within the scope of the designated orphan indication "Treatment of paroxysmal nocturnal haemoglobinuria".

Intention to diagnose, prevent or treat

With reference to the positive CHMP benefit-risk assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

The COMP has previously acknowledged that the condition is life-threatening and chronically debilitating due to the complications of the chronic haemolysis such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications at the level of the central nervous system are the most common cause of death. This is still relevant.

Number of people affected or at risk

The applicant estimated the lower and higher numbers of PNH cases using the prevalence reported directly in one publication (Hill, 2006 [lower estimate]), and the prevalence estimated from incidence in one other publication (Morado, 2017 [higher estimate]), applied to country population denominators. A conclusion of 0.159 to 0.306 per 10,000 was provided.

The COMP has previously considered a less than 0.2 at the time of this designation, which may be retained for this procedure.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The only product authorized in the European Union for the treatment of PNH is Eculizumab, an orphan medicinal product. Eculizumab is currently indicated for patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.

Significant benefit

Alexion received protocol assistance including answers to questions on significant benefit. The proposal was to base the significant benefit rationale on a clinically relevant advantage supported with clinical data on haemolysis as measured by normalization of LDH and the proportion of patients with breakthrough haemolysis. The COMP at that time had recommended reconsidering the above proposal, because a non-inferiority design with an active comparator with the same mechanism of action was not expected to generate data to support the significant benefit based on a clinically relevant advantage.

At the time of marketing authorisation, the sponsor provided two arguments for the justification of significant benefit, one for improved haemolysis and breakthrough events, and a second one based on the reduction of the number of infusions:

- The applicant firstly argued a clinically relevant advantage of improved efficacy, which nevertheless has not been confirmed by the non-inferiority studies presented for MA.

In more detail, and with regards to study 301, it was argued that the LDH profile observed over time was similar to eculizumab but with consistently lower mean LDH levels in the ravulizumab arm. At Day 183, the adjusted prevalence of LDH-N was 53.6% for the ravulizumab group and 49.4% for the eculizumab group. The adjusted OR excluding baseline LDH as an explanatory variable for the comparison of ravulizumab to eculizumab was 1.187 (0.796, 1.769) indicating that a patient switching to ravulizumab had a nearly 19% increased probability of achieving LDH-N compared to a patient who

received eculizumab. The median time to first LDH-N was 24 days (22, 29) for ravulizumab and 29 days (24, 43) for eculizumab, and the difference of 5 days favored ravulizumab.

With regards to study 302, it was pointed out that the LDH profile observed over time was similar to eculizumab with generally lower mean LDH levels in the ravulizumab arm. At Day 183, LDH-N was achieved by 64 of 97 (66.0%) patients treated with ravulizumab and 58 of 98 (59.2%) patients treated with eculizumab. The adjusted OR from the GEE model excluding baseline LDH as an explanatory variable for the comparison of ravulizumab to eculizumab was 1.179 (0.737, 1.887) indicating that a patient switching to ravulizumab had a nearly 18% increased probability of achieving LDH-N compared to a patient who remained on eculizumab. As discussed above, in light of the non-inferiority shown in all endpoints of both these studies, an improved LDH effect for the purpose of justifying SB is not endorsed.

Another argument by the sponsor refers to reduction of breakthrough events in the two studies, but this was again not supported by the clinical data. It was argued that in study 301, the difference between treatment groups in the proportion of patients who experienced breakthrough haemolysis was 6.7% (–14.21%, 0.18%), nevertheless the upper bound of the 95% CI was less than the protocol specified NIM of 20%. It was also argued that fewer ravulizumab-treated patients (4.0%, n = 5 with 5 events) experienced breakthrough events during the Primary Evaluation Period compared with eculizumab-treated patients (10.7%, n = 13 with 15 events), representing more than a 2-fold difference between treatment groups. In Study 302, it was also stated that none of the patients in the ravulizumab group experienced breakthrough haemolysis during the Primary Evaluation Period compared with 5 (5.1%) patients in the eculizumab group. The difference between treatment groups in the proportion of patients who experienced breakthrough haemolysis was 5.1% (18.99%, 8.89%). The upper bound was less than the protocol-specified NIM of 20%. In all cases the effects observed are comparable and trends do not support improved efficacy in any endpoints.

An additional post hoc analysis of the breakthrough hemolysis of the 301 study was also provided based on the following:

1. Number of breakthrough events (BTH events) allowing to have more precision and information on the number of events per year compared to the number of cases.
2. Percentage of breakthrough haemolysis using only the LDH portion of the breakthrough haemolysis definition (BTH-only).
3. Percentage of patients with free C5 levels >0.5 ug/mL used as a response indicator.
4. Number of transfusion units (units-Tx) used as a response predictor which is an alternative to transfusion avoidance endpoints.

The relevance of these endpoints for a clinically relevant advantage has not been justified and would require further elaboration.

Table 1. From the sponsor's application

End point	Ravulizumab (N=125)	Eculizumab (N=121)	Estimated Difference (ravulizumab -eculizumab)	95% CI (LB, UB)	Nominally Superior?
BTH (events)	6.8/100 PY (2.17, 21.46)	21.5/100 PY (8.91, 51.74)	0.32[(1)]	0.11, 0.92	Yes
BTH-LDH only	8.8% (3.83, 13.77)	20.7% (13.45, 27.88)	- 11.7%	- 20.7%, - 2.7%	Yes
Free C5 > 0.5 µg/mL	0.0% (0.00, 2.91)	12.4% (7.11, 19.62)	- 12.3%	- 18.2%, - 6.5%[(2)]	Yes
Units-Tx	1.25 units (0.62, 1.89)	1.82 units (1.17, 2.47)	- 0.57	- 1.48, 0.34	No

- There was a second argument of major contribution to patient care based on the reduction of infusions (every 2 weeks vs every 8 weeks). The applicant noted that the pivotal clinical studies provide favourable results for ravulizumab over eculizumab in quality-of-life instruments but did not show statistically significant differences in EORTC-QLQ-C30 and FACIT-Fatigue scores between ravulizumab and eculizumab.

The applicant has conducted a sub-study (PNH-302s) to Evaluate Patient Preference for the Treatment of Paroxysmal Nocturnal Hemoglobinuria, from patients currently enrolled in Study ALXN1210-PNH-302. The primary and secondary objectives are respectively: to evaluate patient preference for eculizumab (q2w) or ravulizumab (q8w) treatment and identify characteristics contributing to patient's preference for treatment with eculizumab or ravulizumab. Interim results showed that the majority of patients (49 out of 52 patients, 94%) preferred ravulizumab. Patients reported which medication they preferred based on 9 treatment factors (controlling fatigue; controlling symptoms other than fatigue; frequency of infusions; side effects of treatment; convenience of receiving treatment; being able to plan activities; effectiveness of the medication until the next infusion; anxiety related to the infusion; your overall quality of life). At least 50% of patients preferred ravulizumab for all factors except "side effects of treatment." For "side effects of treatment," 26 patients (50%) preferred ravulizumab and an equal number indicated no preference. The factors for which the greatest proportions of patients preferred ravulizumab were "frequency of infusions" and "being able to plan activities" (each with 51 patients, 98%) and "convenience of receiving treatment" (48 patients, 92%). In addition, patients reported which factor was the most important in deciding which medication they preferred overall. The factors chosen as most important by the largest numbers of patients were "frequency of infusions" (22 patients) and "overall quality of life" (10 patients). The only factors that were not chosen by any patient were "anxiety related to the infusion" and "side effects of treatment".

Such claims are to be considered with caution, as preferences or convenience do not constitute per se documentation of a major contribution of patient care. For instance, the claim of the reduction in the number of infusions per year (26 for eculizumab to 6 for ravulizumab), has to be put in the context of the same route of administration and the time spent in hospital, not merely the number of hospitalisations. Eculizumab is to be administered over 25 – 45 minutes in adults and 1-4 hours in paediatric patients, while ravulizumab over "a minimal period of 1.7 to 2.4 hours".

It was also noted that when the sponsor collected PROs from the study, no significant differences ensued in EORTC-QLQ-C30 and FACIT-Fatigue scores.

The sponsor was requested to document any claims of significant benefit in an OE before the COMP.

4. COMP list of issues

Significant benefit

The sponsor argues both a clinically relevant advantage based on improved efficacy, as well as a major contribution to patient care based on the reduced number of infusions.

Non-inferiority with regards to all studied endpoints of the main clinical studies does not allow for a consideration of improved efficacy. Moreover, when the sponsor collected PROs from a specific study, no significant differences ensued in EORTC-QLQ-C30 and FACIT-Fatigue scores.

The sponsor is invited to provide data to justify a clinically relevant advantage or major contribution to patient care. Data from patients who have experienced both treatments would be helpful in that regard.