EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Ultomiris 300 mg/3ml
Ultomiris 1100 mg/11ml

Date: September 2024

Unit: Technical Assessment Unit

Assessment report

Ultomiris

Administrative information:

Trade name of the medicinal product:	Ultomiris 300mg/3ml Ultomiris 1100mg/11 ml
INN (or common name) of the active substance(s):	Ravulizumab
Manufacturer of the finished product	• Alexion Pharma International Operations Limited, Alexione Atholone Manufacturing Facility (AAMF) Monksland Industrial Estate Athlone Co. Roscommon N37 DH79, Ireland. • Catalent Indiana LLC, 1300 S Patterson Dr Bloomington, IN 47403 US
Marketing Authorization holder	Alexion Europe SAS, located at 103-105 rue Anatole France, 92300 Levallois Perret, France.
Applied Indication(s):	- Paroxysmal nocturnal haemoglobinuria (PNH) - Atypical haemolytic uremic syndrome (aHUS) - Generalised myasthenia gravis (gMG) - Neuromyelitis optica spectrum disorder (NMOSD)
Pharmaceutical form(s) and strength(s):	Drug product is supplied as a sterile aqueous solution for intravenous administration containing ravulizumab at a concentration of 100 mg/mL

Route of administration	intravenous (IV) administration
Approved pack	• Carton box containing 3 ml of sterile concentrate in a vial (type 1 glass) with a stopper and seal and an inner leaflet. • Carton box containing 11 ml of sterile concentrate in a vial (type 1 glass) with a stopper and seal and an inner leaflet.

List of abbreviations:

EMA	European medicines Agency
CTD	Common Technical Document
AI	Active ingredient
IgG	Immunoglobulin G
EU	European union
US	United states
PNH	Paroxysmal nocturnal hemoglobinuria
gMG	generalized myasthenia gravis
NMOSD	Neuromyelitis optica spectrum disorder
aHUS	Atypical haemolytic uremic syndrome
ADMF	Alexion Dublin Manufacturing Facility
AAMF	Alexione Atholone Manufacturing Facility
C5	complement component 5
GCP	Good Clinical practice
PD	pharmacodynamics
PK	pharmacokinetics

Dossier initial submission and evaluation process:

- The product was submitted for registration via reliance level I.
- The dossier evaluation by the registration administration units was started on 2.10.2023 after providing all the required documents (EMA detailed unredacted assessment report along with Full CTD for the product)

1. **General introduction about the product including brief description of the AI, its mode of action and indications**:

-Ultomiris 300 & 1100 are supplied as a sterile aqueous solution for intravenous administration containing ravulizumab at a concentration of 100 mg/mL in 50 mM sodium phosphate, 25 mM L-arginine, 5% (w/v) sucrose, 0.05% (w/v) Polysorbate 80, and formulated to pH 7.4 in stoppered 3- and 11-mL glass vials. The product is designed for infusion by diluting into commercially available normal saline (0.9% sodium chloride).

-Ravulizumab is a humanized monoclonal IgG2/4 kappa antibody which binds to the human complement protein C5 blocking its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b.

- Ravulizumab was designed to provide immediate, complete, and sustained inhibition of terminal complement activation, with same mechanism of action as eculizumab (C5 inhibition). The main goal of ravulizumab treatment is to minimize the risk of intravascular hemolysis over an extended dosing interval compared to eculizumab.

***Eculizumab (Soliris®), approved in 2007 in the EU and US, in 2010 in Japan, and subsequently in many countries globally, is the first approved drug and current standard-of-care for PNH ,in 2017 for gMG, in 2019 for NMOSD & for aHUS in 2011

2. **Quality aspects:**

- **Manufacturer(s):**

Drug substance:

Active substance is manufactured at both Lonza Biologics-spain & Alexion Pharma International Operations Limited –Ireland (ADMF)

Drug product:

Finished product is manufactured at both Alexion Pharma International Operations Limited (AAMF) –Ireland & Catalent Indiana LLC- US

- **Stability**

-Based on available stability data,

Drug substance:

- **Approved Storage Conditions of the active substance:**
  -18 months stored at 2 – 8°C or 30 months stored at -25 to -15°C Protected from light
- **Approved shelf life for the active substance:**
  -18 months stored at 2 – 8°C or 30 months stored at -25 to -15°C

Drug product:

- **Approved Storage Conditions of the finished product:**

-Store in a refrigerator (2°C–8°C)
-Do not freeze.
-Keep the vial in the outer carton in order to protect from light.
After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product has been demonstrated for up to 24 hours at 2 °C-8 °C and up to 4 hours at room temperature.

- **Approved shelf life for the finished product:**

-18 months

3. Non-clinical and clinical aspects:

- Ravulizumab provides immediate, complete, and sustained C5 inhibition, and ameliorates intravascular hemolysis and associated clinical consequences in both complement inhibitor-naïve and eculizumab-experienced pediatric patients with PNH. Importantly, ravulizumab protects pediatric patients with PNH from the devastating sequelae of intravascular hemolysis, reduces the need for transfusions, reduces BTH events, and enables improved QoL.
-The main safety concern for ravulizumab, meningococcal infection, is common to all C5 inhibitors and can be effectively managed with the risk mitigation strategies already in place for ravulizumab. Similarly, the other risk mitigations measures already in place for pediatric patients treated with C5 inhibitors, including measures addressing the potential safety risk of serious infections with a required vaccination against Haemophilus influenzae and pneumococcal infections, also apply to pediatric PNH patients treated with ravulizumab.
- From a non-clinical point of view, pharmacologic and toxicological characterization is acceptable. Non-clinical data reveal no special hazard for humans based on nonclinical studies using a murine surrogate molecule, BB5.1, in mice.
-The Clinical trials were performed in accordance with GCP as claimed by the applicant.

-The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.
-Four Phase I studies were conducted in healthy volunteers to collect data on safety, tolerability, immunogenicity, PK and PD. A Phase 1b and a Phase 2 dose escalation studies were conducted for dose selection in patients with PNH who were naïve to complement inhibitor treatment. Two Phase 3 studies were conducted as pivotal studies, one in patients with PNH who were naïve to complement inhibitor treatment and other in patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.
-overall the clinical data from the Phase 3 pediatric study demonstrate a favourable benefit-rislk profile for treatment with ravulizumab in pediatric patients with PNH

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/ultomiris-epar-public-assessment-report_en.pdf