EMA/380480/2023

European Medicines Agency decision

P/0353/2023

of 8 September 2023

on the acceptance of a modification of an agreed paediatric investigation plan for ravulizumab (Ultomiris), (EMEA-002077-PIP01-16-M06) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0199/2017 issued on 14 July 2017, the decision P/0356/2017 issued on 1 December 2017, the decision P/0166/2019 issued on 15 May 2019, the decision P/0399/2020 issued on 23 October 2020, the decision P/0239/2021 issued on 17 June 2021 and the decision P/0191/2022 issued on 10 June 2022,

Having regard to the application submitted by Alexion Europe SAS on 20 April 2023 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 21 July 2023, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to the agreed paediatric investigation plan and to the deferral.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan, including changes to the deferral.

[1] OJ L 378, 27.12.2006, p.1, as amended.
[2] OJ L 136, 30.4.2004, p. 1, as amended.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for ravulizumab (Ultomiris), solution for injection, concentrate for solution for infusion, subcutaneous use, intravenous use, including changes to the deferral, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Alexion Europe SAS, 103-105 rue Anatole France, 92300 - Levallois-Perret, France.

EMA/PDCO/192651/2023
Amsterdam, 21 July 2023

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-002077-PIP01-16-M06

Scope of the application

Active substance(s):

Ravulizumab

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of paroxysmal nocturnal haemoglobinuria

Pharmaceutical form(s):

Solution for injection

Concentrate for solution for infusion

Route(s) of administration:

Subcutaneous use

Intravenous use

Name/corporate name of the PIP applicant:

Alexion Europe SAS

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Alexion Europe SAS submitted to the European Medicines Agency on 20 April 2023 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0199/2017 issued on 14 July 2017, the decision P/0356/2017 issued on 1 December 2017, the decision P/0166/2019 issued on 15 May 2019, the decision P/0399/2020 issued on 23 October 2020, the decision P/0239/2021 issued on 17 June 2021 and the decision P/0191/2022 issued on 10 June 2022.

The application for modification proposed changes to the agreed paediatric investigation plan and to the deferral.

The procedure started on 22 May 2023.

Scope of the modification

Some timelines of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree to changes to the paediatric investigation plan and to the deferral in the scope set out in the Annex I of this opinion.

  The Paediatric Committee member of Norway agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annexes and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

Not applicable

2. Paediatric investigation plan

2.1. Condition:

Treatment of paroxysmal nocturnal haemoglobinuria (PNH)

2.1.1. Indication(s) targeted by the PIP

Treatment of paroxysmal nocturnal haemoglobinuria

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Concentrate for solution for infusion

Solution for injection

2.1.4. Measures

Area	Description
Quality-related studies	**Study 5** *(same study as Study 4 in 001943-PIP01-16-M05 and subsequent modifications thereof)* *(This study was added as a result of procedure 002077-PIP01-16-M03.)* Development of an age-appropriate subcutaneous formulation
Non-clinical studies	Not applicable
Clinical studies	**Study 1 (ALXN1210-PNH-304)** Open-label, multicentre, single arm trial to evaluate pharmacokinetic (PK) and pharmacodynamic (PD) parameters, efficacy and safety of ravulizumab in children less than 18 years of age with PNH **Study 6 (ALXN1210-PED-316)** *(same study as Study 5 in 001943-PIP01-16-M05 and subsequent modifications thereof)* *(This study was added as a result of procedure 002077-PIP01-16-M03.)*

	Open label multi-centre study to evaluate pharmacokinetics, pharmacodynamics, activity and safety of ravulizumab following subcutaneous administration in children from 2 years to less than 18 years of age with atypical haemolytic uraemic syndrome (aHUS) or PNH
Extrapolation, modelling and simulation studies	**Study 2** *(same study as Study 3 in 001943-PIP01-16-M05 and subsequent modifications thereof)* Modelling and simulation study to evaluate the use of intravenous ravulizumab in children from birth to less than 18 years of age **Study 3** Extrapolation study to evaluate the efficacy, PK/PD and safety of ravulizumab in paediatric PNH patients from 12 to less than 18 years of age **Study 4** Extrapolation study to evaluate the efficacy, PK/PD and safety of ravulizumab in paediatric PNH patients from birth to less than 12 years of age **Study 7** *(same study as Study 6 in 001943-PIP01-16-M05 and subsequent modifications thereof)* *(This study was added as a result of procedure 002077-PIP01-16-M03.)* Modelling and simulation study to evaluate the use of subcutaneous ravulizumab in PNH and aHUS in children from 2 years to less than 18 years of age **Study 8** *(same study as Study 7 in 001943-PIP01-16-M05 and subsequent modifications thereof)* *(This study was added as a result of procedure 002077-PIP01-16-M03.)* Extrapolation study to evaluate the use of subcutaneous ravulizumab in children from 2 years to less than 18 years of age with aHUS or paroxysmal nocturnal haemoglobinuria (PNH)
Other studies	Not applicable
Other measures	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By December 2025
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

Condition(s) and authorised indication(s)

1. Treatment of paroxysmal nocturnal haemoglobinuria (PNH)

Authorised indication(s):

- Treatment of adult and paediatric patients with a body weight of 10 kg or above 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.
  - Invented name(s):

    Ultomiris 300 mg/3 mL concentrate for solution for infusion

    Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

    Ultomiris 300 mg/30 mL concentrate for solution for infusion
  - Authorised pharmaceutical form(s): Concentrate for solution for infusion
  - Authorised route(s) of administration: Intravenous use
  - Authorised via centralised procedure
- 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.
  - Invented name(s):

    Ultomiris 245 mg solution for injection in cartridge
  - Authorised pharmaceutical form(s): solution for injection (on-body injector)
  - Authorised route(s) of administration: subcutaneous use
  - Authorised via centralised procedure

2. Treatment of atypical haemolytic uremic syndrome (aHUS)

Authorised indication(s):

- Treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.
  - Invented name(s):

    Ultomiris 300 mg/3 mL concentrate for solution for infusion

    Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

    Ultomiris 300 mg/30 mL concentrate for solution for infusion

- Authorised pharmaceutical form(s): Concentrate for solution for infusion
- Authorised route(s) of administration: Intravenous use
- Authorised via centralised procedure

- Treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.
  - Invented name(s): Ultomiris 245 mg solution for injection in cartridge
  - Authorised pharmaceutical form(s): solution for injection (on-body injector)
  - Authorised route(s) of administration: subcutaneous use
  - Authorised via centralised procedure

3. Treatment of Generalized myasthenia gravis (gMG)

- add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.
  - Invented name(s):

    Ultomiris 300 mg/3 mL concentrate for solution for infusion

    Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

    Ultomiris 300 mg/30 mL concentrate for solution for infusion
  - Authorised pharmaceutical form(s): Concentrate for solution for infusion
  - Authorised route(s) of administration: Intravenous use
  - Authorised via centralised procedure

4. Treatment of Neuromyelitis optica spectrum disorder (NMOSD)

- Treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive
  - Invented name(s):

    Ultomiris 300 mg/3 mL concentrate for solution for infusion

    Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

    Ultomiris 300 mg/30 mL concentrate for solution for infusion
  - Authorised pharmaceutical form(s): Concentrate for solution for infusion
  - Authorised route(s) of administration: Intravenous use
  - Authorised via centralised procedure