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STUDY REPORT NO. 1122815

PASS INFORMATION

TITLE:	**INTERIM REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
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LINK TO STUDY RECORD IN EU PAS REGISTER:	Not applicable
STUDIED MEDICINAL PRODUCT:	Emicizumab (HEMLIBRA®, ACE910, RO5534262)
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Date and Time(UTC)	Reason for Signing	Name
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ACTIVE SUBSTANCE	Emicizumab (ATC code: B02BX06)
PRODUCT REFERENCE NUMBER:	Not applicable
PROCEDURE NUMBER:	EMEA/H/C/004406
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The main goal of this study is to assess the incidence of thromboembolism (TE), thrombotic microangiopathy (TMA), and anaphylaxis in real-world conditions, in patients exposed to emicizumab and treated at centers participating in the European Haemophilia Safety Surveillance (EUHASS) registry. The primary objective for this study is as follows: • To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products The secondary objectives for this study are as follows: • To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: activated prothrombin complex concentrate (aPCC), recombinant activated factor VII (rFVIIa), and factor VIII (FVIII) products • To describe individual cases of TE and TMA based on available information • To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab • To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information
COUNTRIES OF STUDY POPULATION:	Countries with hemophilia centers participating in the EUHASS Registry: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom

MARKETING AUTHORIZATION HOLDER

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1. SYNOPSIS/ABSTRACT

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SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY

Keywords

Emicizumab, European Haemophilia Safety Surveillance (EUHASS), non-interventional post-authorization safety study (NI-PASS), thromboembolism (TE), thrombotic microangiopathy (TMA).

Rationale and Background

Emicizumab (also known as Hemlibra®, ACE910, and RO5534262) is a humanized monoclonal modified immunoglobulin G4 antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII (FVIII) needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors. As of May 2023, emicizumab is approved in approximately 114 countries worldwide in patients with hemophilia A with FVIII inhibitors and is approved in approximately 102 countries worldwide for the expanded indication to include patients with hemophilia A without FVIII inhibitors, including approval in the US, Japan, and the EU. Two important risks have been identified with the use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: thromboembolic events (TE) and thrombotic microangiopathy (TMA). In addition, one important risk of loss of efficacy due to anti-emicizumab antibodies has been identified with the use of emicizumab alone. Anaphylaxis, anaphylactoid reactions, and systemic hypersensitivity are considered as potential safety risks based on the class of biological drugs.

In order to better assess the incidence of TE, TMA, and anaphylaxis, the Marketing Authorization Holder (MAH) will use information collected by the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program. EUHASS provides the MAH an emicizumab-specific annual report which will be used to calculate the incidence of TE, TMA, and anaphylaxis.

Research Question and Objectives

The main goal of this study is to assess the incidence of TE, TMA, and anaphylaxis under real-world conditions in patients exposed to emicizumab.

The primary objective for this study is as follows:

- To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products

The secondary objectives for this study are as follows:

- To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and concomitantly with each of the following drugs: aPCC, recombinant activated factor VII (rFVIIa), and FVIII product
- To describe individual cases of TE and TMA based on available information
- To summarize the frequency of other adverse events (AEs) collected by EUHASS in patients exposed to emicizumab
- To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information

Amendment and Updates to Protocol

The first version of the protocol was issued on 29 January 2018. There were two subsequent protocol amendments on 7 September 2018 (Version 2) and 8 February 2019 (Version 3).

Study Design

Study GO40162 is a cohort surveillance study based on data provided in the EUHASS emicizumab-specific annual report.

Setting

European Haemophilia Safety Surveillance is a pharmacovigilance program dedicated to monitoring the safety of treatments for people with inherited bleeding disorders across Europe. It is led by European Association for Haemophilia and Allied Disorders (EAHAD) and coordinated by Prof. Dr. [redacted]. Its activities are overseen by an independent Steering Committee. Since its initiation in 2008, EUHASS is used by pharmaceutical companies to conduct post-approval authorization studies. At the start of this study for emicizumab in 2018, 86 participating centers in 27 countries reported information on all the patients they treated, thus minimizing selection bias.

Patients and Study Size (Including Dropouts)

Data from patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS Registry are collected.

The sample size depends on the approval and uptake of emicizumab in the countries with centers participating in the EUHASS Registry.

Variables and Data Sources

The primary variables for this study are as follows:

- TE events
- TMA events
- Anaphylaxis events
- Exposure to emicizumab

The secondary variables for this study are as follows:

- Transfusion transmitted infections
- New inhibitors (antibodies against the coagulation factor)
- Allergic and other acute reactions, with the exception of anaphylaxis
- New malignancy diagnosis
- Death
- Unexpected poor efficacy
- Other AEs possibly related to concentrate/non-factor replacement (NFR), where both concentrate/NFR refer to emicizumab
- Exposure to emicizumab, without replacement factor products in the same calendar year
- Exposure to both aPCC and emicizumab in the same calendar year
- Exposure to both rFVIIa and emicizumab in the same calendar year
- Exposure to both FVIII and emicizumab in the same calendar year

Variables are captured using information from standard patient management. No additional evaluations are done as a consequence of participation in the EUHASS Registry or as a consequence of this study.

Results

During this reporting period (1 January 2021 to 31 December 2021), 1,319 patients were treated with emicizumab alone, 71 patients were treated with emicizumab and NovoSeven, 490 patients were treated with emicizumab and other FVIII (other than Obizur), and 3 patients were treated with emicizumab and factor eight inhibitor bypassing activity (FEIBA). There were no TMA or anaphylaxis events during this reporting period. The following TE events were reported in 2 patients treated with emicizumab:

- A 54-year-old male with a diagnosis of hemophilia A treated with emicizumab alone reported bilateral renal infarcts 7 days after the third loading dose. The patient did not have any thrombotic risk factors reported.

- A 32-year-old male with a diagnosis of hemophilia A treated with emicizumab alone reported a myocardial infarction 11 days after dosing. Risk factors for this patient include smoking, hyperlipidemia, and a body mass index of >30.

A total of 13 other AEs were reported during the current reporting period from 1 January 2021–31 December 2021.

Five patients treated with emicizumab alone reported 7 allergic and other acute reactions:

- A 22-year-old male with a diagnosis of hemophilia A reported pain, swelling, and stiffness in the small joints of fingers in both hands, which was worse in the morning on the day of dosing, which resolved and was considered by the investigator to be possibly related to concentrate/NFR
- A 26-year-old male with a diagnosis of hemophilia A reported a rash 10 days after dosing which resolved and was considered by the investigator to be possibly related to concentrate/NFR.
- An 18-year-old male with a diagnosis of hemophilia A reported headache and dizziness 5 minutes after dosing which resolved and was considered by the investigator to be possibly related to concentrate/NFR.
- A 12-year-old male with a diagnosis of hemophilia A reported rash, painful joints, swollen fingers, and itching 24 hours after dosing which resolved and was considered by the investigator to be definitely related to concentrate/NFR.
- A 24-year-old male with a diagnosis of hemophilia A reported a rash 1 day after dosing which resolved and was considered by the investigator to be definitely related to concentrate/NFR.

Two patients treated with emicizumab alone had a recurrence of FVIII inhibitors:

- Two males aged between 8 and 26 years with a diagnosis of hemophilia A treated with emicizumab alone had a recurrence of FVIII inhibitors.

One patient treated with emicizumab and other FVIII (other than Obizur) had a first occurrence of inhibitor development:

- A male aged between 2 and 4 years with a diagnosis of hemophilia A treated with emicizumab along with other FVIII (other than Obizur) had a first occurrence of inhibitor development.

Three patients treated with emicizumab and other FVIII (other than Obizur) had a recurrence of inhibitors:

- Three males aged between 6 and 55 years with a diagnosis of hemophilia A treated with emicizumab along with other FVIII (other than Obizur) had a recurrence of inhibitors.

From the earliest use of emicizumab in 2017 to 31 December 2021, the sum of total patients treated each year is 2,647 with emicizumab alone, 202 with emicizumab and NovoSeven, 628 with emicizumab and FVIII (other than Obizur), 11 with emicizumab and FEIBA, and 22 with emicizumab and tranexamic acid. Twenty-six AEs were reported, of which 6 were TEs and none were TMA or anaphylaxis events.

Conclusion

Of the patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS Registry during this reporting period, 15 reported an AE. Two patients treated with emicizumab alone reported thrombosis within 30 days of concentrate/NFR. There were no TMA or anaphylaxis events during this reporting period. Additionally, 13 other AEs were reported, where 5 patients treated with emicizumab alone reported 7 allergic and other acute reactions (3 AEs of rash, 2 AEs of arthralgia, 1 AE of headache, and 1 AE of dizziness), 2 patients treated with emicizumab alone had a recurrence of FVIII inhibitors, 1 patient treated with emicizumab and other FVIII (other than Obizur) had a

first occurrence of inhibitor development, and 3 patients treated with emicizumab and other FVIII (other than Obizur) had a recurrence of inhibitors. Based on a review of the available data to date, the safety profile of emicizumab without aPCC/FEIBA in patients with inherited bleeding disorders is acceptable.

Based on the review of currently available data, no new safety signal was detected. An acceptable safety profile was observed that is in line with other published data.

This is the fourth annual report for Study GO40162 and data are still evolving. A full assessment will be made at the final analysis (planned for June 2026), which will include all data collected until 31 December 2024.

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