12 December 2024
EMA/3053/2025
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Adynovi

Rurioctocog alfa pegol

Procedure no: EMEA/H/C/004195/P46/018

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	14 Oct 2024	14 Oct 2024	☐
☐	CHMP Rapporteur Assessment Report	18 Nov 2024	18 Nov 2024	☐
☐	CHMP members comments	02 Dec 2024	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2024	N/A	☐
☒	CHMP adoption of conclusions:	12 Dec 2024	12 Dec 2024	☐

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1. Introduction

On 11th September 2024, the MAH submitted a completed paediatric study for Adynovate (authorised in the EU under the trade name Adynovi), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that TAK-660-5002 was a stand-alone study.

The Company declares that the study results do not require an update to the Product Information of Adynovi.

2.2. Information on the pharmaceutical formulation used in the study

Rurioctocog alfa pegol (ADYNOVATE), is a PEGylated, full-length, recombinant human factor VIII (FVIII) with an extended half-life. It belongs to the pharmacotherapeutic group of coagulation FVIII (Anatomical Therapeutic Chemical code: B02BD02).

In the EU, Adynovi is approved for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency).

Rurioctocog alfa pegol was first licensed in the United States on 13 November 2015 under the trade name ADYNOVATE; it is indicated for on-demand treatment and control of bleeding episodes, routine prophylaxis to reduce the frequency of bleeding episodes, and perioperative management in children and adults with hemophilia A. In the EU, rurioctocog alfa pegol was authorized on 08 January 2018 (under the trade name Adynovi); it is indicated for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study TAK-660-5002,** a multicenter safety and effectiveness study of Adynovate Intravenous administered perioperatively under actual use conditions in routine clinical practice in Japan. This study included 15 patients, one of these patients aged <18 years; hence, this submission was provided to comply with the requirements as stipulated in Article 46 of the European Union (EU) Pediatric Regulation (Regulation [EC] No 1901/2006), as amended.

2.3.2. Clinical study

Study TAK-660-5002

The main objective of this survey was to investigate the safety and effectiveness of ADYNOVATE administered in the perioperative period of surgeries or other invasive procedures such as tooth extractions under actual clinical use conditions.

Patients with FVIII deficiency who received ADYNOVATE for surgery/procedure on or after the start date of this survey were eligible for this survey. It was planned to include 10 patients and 15 surgeries. Patient registration at each site was to be continued until the end of the patient registration period, even after the target number of patients was reached. The observation period was from the start to completion of perioperative management: management from ADYNOVATE administration before (preoperative), during (intraoperative), and after (postoperative) the surgery to completion of the surgical treatment.

Adynovate was administered in the perioperative period of surgeries or other invasive procedures such as tooth extractions under actual clinical use conditions. It was dissolved in 5 mL of the supplied diluent, and slowly injected intravenously. The infusion rate was not to exceed 10 mL/min. The usual dosage is 10 to 30 IU/kg body weight per dose. The dosage could be adjusted according to the patient's condition. For perioperative use, the dose and dosing frequency was to be adjusted to maintain FVIII at the required or higher level depending on the surgery/procedure.

The major survey items collected by the investigators included patient background (including e.g. height, body weight, complications, medical history, severity of haemophilia A, family history of haemophilia A, history of development of FVIII inhibitors), details of treatment (including status of administration of ADYNOVATE and status of administration of concomitant drugs), details of surgery (including diagnosis of the disease requiring surgery, details of the surgery, type of surgery [major/minor], whether or not the surgery was scheduled, date and time of the surgery, amount of bleeding during surgery, blood transfusion, and drainage), effectiveness evaluation (based on a 4-point rating scale [excellent, good, fair, poor] for intraoperative and postoperative [postoperative Day 1 and upon completion of perioperative management or discontinuation of treatment] haemostatic effectiveness, test/observation items (FVIII activity, FVIII inhibitors, and FVIII recovery rate), and adverse events (including date of onset, seriousness, cause of treatment discontinuation, outcome, causal relationship to Adynovate).

Survey period lasted from June 2021 to 31st December 2023, the patient registration period from June 30th 2021 to 31th of August 2023. The survey completion date (final analysis completion date) was on May 15th 2024.

Results

Participant flow

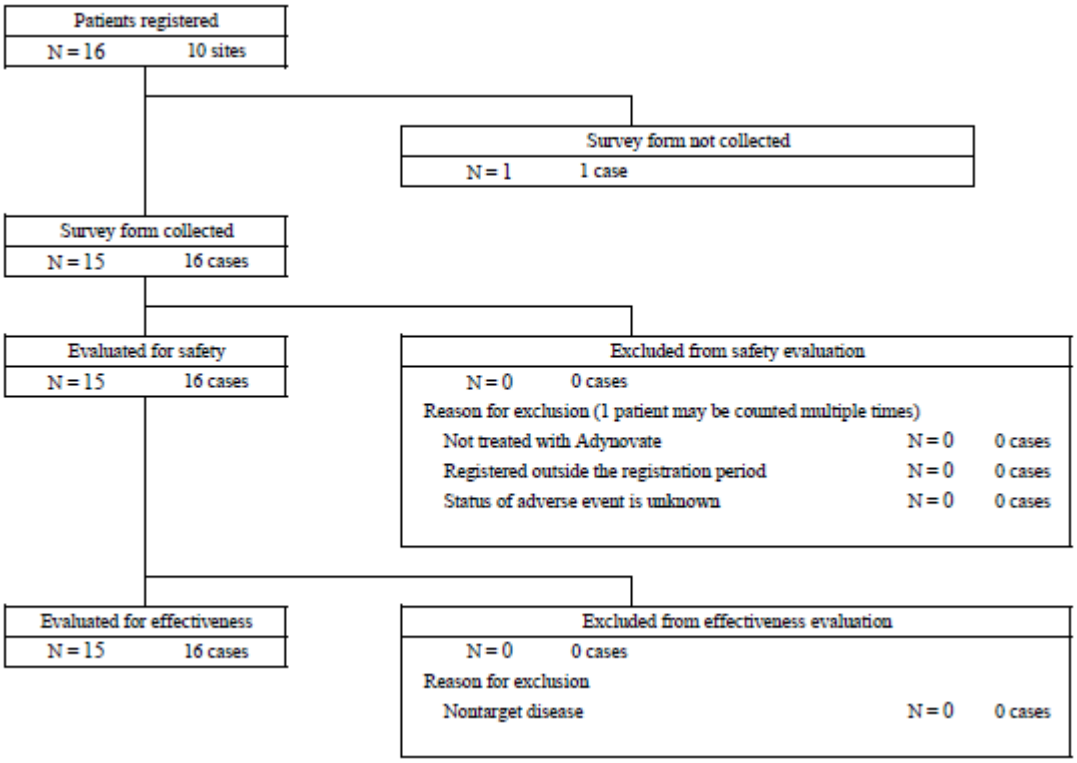

Figure 1: Disposition of patients (patient disposition diagram)

Baseline data

Most patients (93.3%; 14/15) were male. Mean and median ages were 41.4 years and 41.0 years, respectively (range: 12-72 years). Most patients were adults, including 80.0% (12/15) of patients aged 18 to <65 years and 13.3% (2/15) of patients aged ≥65 years; there was **1 paediatric patient** (teenager).

History of surgery was noted in 60.0% (9/15) of patients. Medical history was noted in 40.0% (6/15) of patients. Complications were noted in 86.7% (13/15) of patients. Haemophilia A was categorised as severe in 66.7% (10/15) of patients, moderate in 6.7% (1/15) of patients, and mild in 26.7% (4/15) of patients.

Number analysed

A total of 16 patients were registered from 10 medical institutions in Japan; survey forms were collected from 15 patients. All the patients whose survey forms were collected were evaluated for safety and effectiveness. One paediatric patient was included.

Data from 16 cases of surgeries were reported in this survey. The surgery type was "major" in 25.0% (4/16) of the cases and "minor" in 75.0% (12/16) of the cases.

Intraoperative blood loss was documented in 9 surgeries, with a mean volume of 101.1 mL and median volume of 10.0 mL (range: 0 to 540 mL), but no patient received a blood transfusion during surgery.

Of the 16 cases of surgeries, ADYNOVATE was administered preoperatively in 15 cases, including bolus administration in 14 cases and by continuous infusion in 1 case.

Intraoperative administration of ADYNOVATE was not performed.

Postoperative administration of ADYNOVATE was performed in 16 cases, including 7 cases of routine prophylaxis, 2 cases of continuous infusion, and 7 cases of other treatment methods.

Efficacy results

The haemostatic effectiveness was assessed during surgery, on postoperative Day 1, and at the completion of perioperative management (or discontinuation of treatment) for each surgery.

Of the 16 cases of surgeries in 15 patients who received ADYNOVATE and were evaluated for effectiveness, intraoperative haemostatic effectiveness was not assessed in 1 case in 1 patient. Of the 15 cases in 14 patients evaluated for intraoperative haemostatic effectiveness, the rating was "excellent" in 93.3% (14/15) of cases and "good" in 6.7% (1/15) of cases. No cases were rated as "fair" or "poor".

Of the 16 cases of surgeries in 15 patients who received ADYNOVATE and were evaluated for effectiveness, the haemostatic effectiveness on postoperative Day 1 was assessed as "excellent" in 56.3% (9/16) of cases, "good" in 37.5% (6/16) of cases, and "fair" in 6.3% (1/16) of cases. No cases were rated as "poor".

Of the 16 cases of surgeries in 15 patients who received ADYNOVATE and were evaluated for effectiveness, the haemostatic effectiveness at the completion of perioperative management (or at discontinuation of treatment) was assessed as "excellent" in 50.0% (8/16) of cases, "good" in 43.8% (7/16) of cases, and "fair" in 6.3% (1/16) of cases. No cases were rated as "poor".

Of the 1 case of surgery in the **paediatric patient aged**, the haemostatic effectiveness was rated as "excellent" during surgery, "good" on postoperative Day 1, and "good" at the completion of perioperative management/discontinuation of treatment.

Table 1: Haemostatic effectiveness

Patients Evaluated for Effectiveness

Item		Overall	
		Number (%) of Patients	
		15	
Number of patients evaluated for intraoperative hemostatic effectiveness		14	(93.3)
Intraoperative hemostatic effectiveness*	Excellent	14	(93.3)
	Good	1	(6.7)
	Fair	0	(0.0)
	Poor	0	(0.0)
Number of patients evaluated for postoperative hemostatic effectiveness (postoperative Day 1)		15	(100.0)
Postoperative hemostatic effectiveness* (postoperative Day 1)	Excellent	9	(56.3)
	Good	6	(37.5)
	Fair	1	(6.3)
	Poor	0	(0.0)
Number of patients evaluated for postoperative hemostatic effectiveness (at the completion of perioperative management [or discontinuation of administration])		15	(100.0)
Postoperative hemostatic effectiveness* (at the completion of perioperative management [or discontinuation of administration])	Excellent	8	(50.0)
	Good	7	(43.8)
	Fair	1	(6.3)
	Poor	0	(0.0)

*For each rating of hemostatic effectiveness, the number of surgeries was counted and the percentage was calculated.

Safety results

Overall, 2 patients (13.33%) reported **4 adverse events** in this survey: 1 event each of insomnia, constipation, melaena, and procedural pain. All these events were reported in patients aged 18 years or older.

All 4 adverse events reported occurred during Days 1-5 period and had an outcome of recovered/resolved. One patient (6.67%) reported one serious adverse event of melaena; a causal relationship to ADYNOVATE was ruled out. This event was assessed as "nonserious" by the investigator, but it was regarded as serious because it was categorized under the Important Medical Events List and any event included in that list was to be regarded as "serious" in this survey despite "nonserious" assessment by the investigator.

No patients experienced **adverse reactions**.

2.3.3. Discussion on clinical aspects

The study evaluated the haemostatic effectiveness of ADYNOVATE in 15 patients during and after surgery in 10 medical institutions in Japan. These 15 patients also included one paediatric patient.

Only version 4 of the study protocol (dating 23 August 2023, which corresponds to a time point late into the patient registration period, which ended 31 August 2023) was provided with the submission. It is unclear from the provided data package which amendments were introduced to the protocol at such a late stage. This issue is however not further pursued given that data from only 1 paediatric patient were available from the study, with obvious limitations for the interpretability of the provided data.

Overall, the efficacy results showed that in 14 of the 15 patients (93.3%) the effectiveness was rated as "excellent", with no evaluations indicating "poor" effectiveness.

Of the 1 case of surgery in the **paediatric patient**, the haemostatic effectiveness was rated as "excellent" during surgery, "good" on postoperative Day 1, and "good" at the completion of perioperative management/discontinuation of treatment.

In the safety evaluation, 2 adults (13.33%) reported 4 adverse events, while no adverse reactions occurred in any patients, including the single paediatric patient. There were no incidents of inhibitor development, shock, or anaphylaxis.

As previously stated, the inclusion of only one paediatric patient limits the interpretability of the reported results. No new safety signals in the paediatric population were noted. Based on the provided data the B/R balance of Adynovi remains unchanged. No updates to the PI are deemed necessary based on the provided new data.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.