Review Report

August 7, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	NovoSeven HI Syringe for I.V. Injection 1 mg, NovoSeven HI Syringe for I.V. Injection 2 mg, NovoSeven HI Syringe for I.V. Injection 5 mg
Non-proprietary Name	Eptacog Alfa (Activated) (Genetical Recombination) (JAN*)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	October 30, 2023
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 1.1 mg, 2.1 mg, or 5.2 mg of eptacog alfa (activated) (genetical recombination) to be reconstituted before use.
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	This is an application based on "Handling of Prescription Drugs for Off-label Use" (No. 4 of the Research and Development Division and PMSB/ELD Notification No. 104 dated February 1, 1999).
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the efficacy and safety of the product in controlling bleeding tendency in patients with Glanzmann's thrombasthenia are public knowledge in the fields of medical and pharmaceutical sciences (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below.

Indications

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX
- Control of bleeding tendency in patients with acquired hemophilia
- Control of bleeding tendency in patients with congenital factor VII deficiency

- Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with anti-platelet alloantibodies, with past or present refractoriness to platelet transfusions~~

(Strikethrough denotes a deletion.)

Dosage and Administration

Reconstitute eptacog alfa (activated) (genetical recombination) using the entire amount of the provided dedicated reconstitution solution. Administer the reconstituted solution intravenously over 2 to 5 minutes.

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX

  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate if continued treatment is required. For mild to moderate bleeding, 270 μg/kg (13.5 KIU/kg) may be administered as a single dose.

- Control of bleeding tendency in patients with acquired hemophilia

  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate if continued treatment is required.

- Control of bleeding tendency in patients with congenital factor VII deficiency

  A dose of 15 to 30 μg/kg (0.75-1.5 KIU/kg) should be administered every 4 to 6 hours until hemostasis is achieved. The dose may be adjusted according to the type and severity of the bleeding. The dosing interval may also be adjusted as appropriate.

- Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with anti-platelet alloantibodies, and with past or present refractoriness to platelet transfusions~~

  A dose of 80 to 120 μg/kg (4.0-6.0 KIU/kg) should be administered every 1.5 to 2.5 hours until hemostasis is achieved and clinical improvement is observed.

(Strikethrough denotes a deletion.)

** Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

July 3, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	NovoSeven HI Syringe for I.V. Injection 1 mg, NovoSeven HI Syringe for I.V. Injection 2 mg, NovoSeven HI Syringe for I.V. Injection 5 mg
Non-proprietary Name	Eptacog Alfa (Activated) (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	October 30, 2023
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 1.1 mg, 2.1 mg, or 5.2 mg of eptacog alfa (activated) (genetical recombination) to be reconstituted before use.

Proposed Indications

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX
- Control of bleeding tendency in patients with acquired hemophilia
- Control of bleeding tendency in patients with congenital factor VII deficiency
- Control of bleeding tendency in patients with Glanzmann's thrombasthenia with ~~anti-platelet alloantibodies, and with~~ past or present refractoriness to platelet transfusions

(Strikethrough denotes a deletion.)

Proposed Dosage and Administration

Reconstitute eptacog alfa (activated) (genetical recombination) using the entire amount of the provided dedicated reconstitution solution, and administer the prepared solution intravenously over 2 to 5 minutes.

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX

  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate if continued treatment is required. For mild to moderate bleeding, 270 μg/kg (13.5 KIU/kg) may be administered as a single dose.

- Control of bleeding tendency in patients with acquired hemophilia
  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate if continued treatment is required.

- Control of bleeding tendency in patients with congenital factor VII deficiency
  A dose of 15 to 30 μg/kg (0.75-1.5 KIU/kg) should be administered every 4 to 6 hours until hemostasis is achieved. The dose may be adjusted according to the type and severity of the bleeding. The dosing interval may also be adjusted as appropriate.

- Control of bleeding tendency in patients with Glanzmann's thrombasthenia with ~~anti-platelet alloantibodies, and with~~ past or present refractoriness to platelet transfusions
  A dose of 80 to 120 μg/kg (4.0-6.0 KIU/kg) should be administered every 1.5 to 2.5 hours until hemostasis is achieved and clinical improvement is observed.

(Strikethrough denotes a deletion.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Eptacog alfa (activated) (genetical recombination) (hereinafter, "eptacog alfa") is the active ingredient of a recombinant activated coagulation factor VII formulation, and has been approved for the following indications: "Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX," "Control of bleeding tendency in patients with acquired hemophilia," "Control of bleeding tendency in patients with congenital factor VII deficiency," and "Control of bleeding tendency in patients with Glanzmann's thrombasthenia with anti-platelet alloantibodies, and with past or present refractoriness to platelet transfusions." It has been approved in more than 90 countries or regions including the United States (US) and Europe.

Glanzmann's thrombasthenia (GT) is an autosomal recessive bleeding disorder due to impaired platelet aggregation as a result of deficient or abnormal platelet membrane glycoprotein (GP) IIb-IIIa. GT is classified into 3 types: Type I (GP IIb-IIIa expression of <5% of the normal level), Type II (GP IIb-IIIa expression of 5% to 20% of the normal level), and a variant type (qualitative abnormality of GP IIb-IIIa). The prevalence of GT is generally estimated to be approximately 1/1,000,000, and is known to be higher in specific ethnic groups such as Arabs and Persians (*Clin Appl Thromb Hemost*. 2009;15:152-65). It has been reported to be 1/100,000 to 1/400,000 in the 6 Persian Gulf countries comprising the Gulf Cooperation Council (*J Appl Hematol*. 2019;10:1-9). GT patients are treated by such methods as local compression and antiplasmins in case of mild bleeding, and by platelet transfusion in case of serious bleeding and surgery. However, repeated platelet transfusion is known to induce the development of alloantibodies against platelet or human leukocyte antigen (HLA), which may cause refractoriness to platelet transfusions. According to the relevant website, eptacog alfa is recommended for use in patients with refractoriness to platelet transfusions (https://www.shouman.jp/disease/details/09_20_033/, Information Center for Specific Pediatric Chronic Diseases, Japan [last accessed on July 3, 2024]).

The indication of eptacog alfa for GT was initially approved as an additional indication for preceding products, namely, NovoSeven for Injection 1.2 mg and another product with a different strength, and NovoSeven HI for Intravenous Injection 1 mg and 2 other products with different strengths, in June 2011. The present application is a public knowledge-based application submitted in accordance with the notification titled "Prior Assessment at the Pharmaceutical Affairs and Food Sanitation Council" (PFSB/ELD Notification No. 1025-9 dated October 25, 2010). The latest approval status in Europe[1)] at the time was used as reference in prior assessments by the then Pharmaceutical Affairs and Food Sanitation Council and reviews by PMDA. Outside of Japan, a registry survey [see Section 7.1.1] was subsequently conducted as part of the post-marketing commitments imposed by the European regulatory authorities. On the basis of the survey results, the condition of the status of anti-platelet alloantibodies was deleted from the indication for GT in Europe in 2018, and a change was simultaneously made to permit the use of eptacog alfa when platelets are not readily available.[2)] In the US, an

1) In Europe, eptacog alfa was approved for the following indications in 2004: "The treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: in patients with Glanzmann's thrombasthenia with antibodies to GP IIb-IIIa and/or HLA, and with past or present refractoriness to platelet transfusions."

2) The indication in Europe after the change was "the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: in patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available," and remains the same at present.

application for the indication of GT, which included the results of the above survey, was submitted, and eptacog alfa was approved without the condition of the status of anti-platelet alloantibodies in 2014.[3)]

Under the above circumstances, the Japanese Society on Thrombosis and Hemostasis submitted a petition to the Ministry of Health, Labour and Welfare in December 2022. The petition concerned the use of eptacog alfa in GT patients, and proposed deletion of the condition of the status of anti-platelet alloantibodies, and to permit its use even when platelets are not readily available.

The applicant closely reviewed the application data submitted in Europe and the information necessary for the regulatory submission in Japan, namely, the results of the above-mentioned registry survey, the results of an observational study conducted in Japan, published articles, and other information. As a result of the review, the applicant concluded that the content of the petition is public knowledge in the fields of medical and pharmaceutical sciences, even without conducting additional clinical studies, and submitted a partial change application for eptacog alfa for the content of the petition based on "Handling of Prescription Drugs for Off-label Use" (No. 4 of the Research and Development Division and PMSB/ELD Notification No. 104 dated February 1, 1999).

2. Quality and Outline of the Review Conducted by PMDA

Since the present application concerns new indications and new dosages, "data relating to quality" were not submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application concerns new indications and new dosages, no new data were submitted in this section, because "non-clinical pharmacology data" had been evaluated during the review process for the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application concerns new indications and new dosages, no new data were submitted in this section, because "non-clinical pharmacokinetic data" had been evaluated during the review process for the initial approval.

5. Toxicology and Outline of the Review Conducted by PMDA

Since the present application concerns new indications and new dosages, "data relating to toxicity" were not submitted.

[3)] The indication in the US is "treatment of bleeding episodes and perioperative management in adults and children with Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets."

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although the present application concerns new indications and new dosages, no new data were submitted in this section, because "data relating to biopharmaceutics and associated analytical methods" and "clinical pharmacology data" had been evaluated during the review process for the initial approval.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

In the present application, no evaluation data were submitted. The results of the registry survey and the observational study shown in Table 1 were submitted as reference data. Information in management guidelines and published articles was also submitted.

Table 1. Main data submitted for the present application

Data category	Region	Study ID	Population	No. of enrolled patients	Study period
Reference	Foreign	Registry survey (Study F7HAEM-3521)	GT patients	218	December 2004 to December 2011
	Japan	Observational study (Study F7HAEM-4030)	GT patients	4	June 2013 to June 2017

7.1 Foreign registry survey and Japanese observational study

7.1.1 Foreign registry survey (CTD 5.3.5.4-1: Study F7HAEM-3521, December 2004 to December 2011, reference data)

The efficacy and safety of eptacog alfa in the treatment of bleeding episodes and the hemostatic management of surgery in GT patients were investigated in a survey (Study F7HAEM-3521) using the Glanzmann's thrombasthenia registry (GTR), a prospective registry of data collected in 15 countries including France, Algeria, and the Netherlands.

Of 218 patients registered in the GTR, 133 patients received eptacog alfa during 492 times of hospitalization (dose per administration [mean ± standard deviation]: 98 ± 42 μg/kg/dose for the treatment of bleeding episodes and 107 ± 39 μg/kg/dose for the hemostatic management of surgery). Of them, 94 patients received eptacog alfa for the treatment of bleeding episodes during 333 times of hospitalization and 77 patients used eptacog alfa for the hemostatic management of surgery during 159 times of hospitalization. Age (mean [range]) at the initial administration of eptacog alfa was 24.1 [0-80] years; 41 patients (30.8%) were aged <12 years, 16 patients (12.0%) were aged 12 to 17 years, 74 patients (55.6%) were aged ≥18 years, and the age of 2 patients (1.5%) was unknown. Among the patients who received eptacog alfa, the disease type was Type I in 62 patients (46.6%), Type II in 13 patients (9.8%), the variant type in 3 patients (2.3%), and unknown in 55 patients (41.4%); refractoriness to platelet transfusions was present in 31 patients (23.3%), absent in 63 patients (47.4%), and unknown in 39 patients (29.3%); anti-platelet antibodies was present in 60 patients (45.1%), absent in 65 patients (48.9%), and unknown in 8 patients (6.0%).

Table 2 and Table 3 show the efficacy of eptacog alfa by concomitant treatment as well as by the status of refractoriness to platelet transfusions and the status of anti-platelet antibodies in the treatment of bleeding

episodes and the hemostatic management of surgery in patients treated with eptacog alfa. Table 4 shows the reported adverse events.

Table 2. Efficacy in the treatment of bleeding episodes in patients treated with eptacog alfa

		No. of patients	No. of bleeding episodes	Efficacy in bleeding episodes[a)]			
				Effective	Partially effective	Ineffective	Unevaluable/ unknown
Entire population		94	333	262 (78.7)	60 (18.0)	4 (1.2)	7 (2.1)
By concomitant treatment							
Without concomitant treatments		38	155	129 (83.2)	24 (15.5)	0	2 (1.3)
Platelet transfusion		10	14	12 (85.7)	1 (7.1)	0	1 (7.1)
Platelet transfusion + other hemostatic treatment		34	54	35 (64.8)	18 (33.3)	1 (1.9)	0
Other hemostatic treatment than platelet transfusion		55	110	86 (78.2)	17(15.5)	3(2.7)	4 (3.6)
By the status of refractoriness to platelet transfusions and the status of anti-platelet antibodies							
Refractoriness, present	Antibodies, present	15	36	26 (72.2)	10 (27.8)	0	0
	Antibodies, absent	5	31	23 (74.2)	6 (19.4)	1 (3.2)	1 (3.2)
	Unknown	1	6	6 (100)	0	0	0
Refractoriness, absent	Antibodies, present	14	47	30 (63.8)	12 (25.5)	2 (4.3)	3 (6.4)
	Antibodies, absent	29	159	135 (84.9)	22 (13.8)	0	2 (1.3)
	Unknown	5	9	5 (55.6)	4 (44.4)	0	0
Refractoriness, unknown	Antibodies, present	10	14	11 (78.6)	2 (14.3)	1 (7.1)	0
	Antibodies, absent	13	27	22 (81.5)	4 (14.8)	0	1 (3.7)
	Unknown	2	4	4 (100)	0	0	0

No. of patients, No. of episodes, or No. of episodes (%)

a) Effective, hemostasis achieved or no bleeding for ≥6 hours; partially effective, bleeding reduced but persisting; ineffective, bleeding unchanged or worsened.

Table 3. Efficacy in the hemostatic management of surgery in patients treated with eptacog alfa

		No. of patients	No. of cases of hemostatic management of surgery	Efficacy in the hemostatic management of surgery[a)]			
				Effective	Partially effective	Ineffective	Unevaluable/ unknown
Entire population		77	159	140 (88.1)	14 (8.8)	3 (1.9)	2 (1.3)
By concomitant treatment							
Without concomitant treatments		35	62	59 (95.2)	3 (4.8)	0	0
Platelet transfusion		4	4	4 (100)	0	0	0
Platelet transfusion + other hemostatic treatment		19	22	15 (68.2)	4 (18.2)	2 (9.1)	1 (4.5)
Other hemostatic treatment than platelet transfusion		42	71	62 (87.3)	7 (9.9)	1 (1.4)	1 (1.4)
By the status of refractoriness to platelet transfusions and the status of anti-platelet antibodies							
Refractoriness, present	Antibodies, present	16	40	38 (95.0)	2 (5.0)	0	0
	Antibodies, absent	5	12	8 (66.7)	4 (33.3)	0	0
	Unknown	1	1	1 (100)	0	0	0
Refractoriness, absent	Antibodies, present	13	25	21 (84.0)	2 (8.0)	1 (4.0)	1 (4.0)
	Antibodies, absent	19	37	35 (94.6)	1 (2.7)	1 (2.7)	0
	Unknown	1	1	1 (100)	0	0	0
Refractoriness, unknown	Antibodies, present	10	20	14 (70.0)	4 (20.0)	1 (5.0)	1 (5.0)
	Antibodies, absent	12	23	22 (95.7)	1 (4.3)	0	0
	Unknown	0	0	0	0	0	0

No. of patients, No. of cases, or No. of cases (%)

a) Effective, normal hemostasis; partially effective, mild bleeding tendency; ineffective, excessive bleeding tendency.

Table 4. Adverse events reported in the foreign registry survey

Patient[a)]	Refractoriness to platelet transfusions	Anti-platelet antibodies	Adverse events	Seriousness	Causal relationship to eptacog alfa	Outcome
A (5[redacted] years of age, male)	Absent	Absent	Allergic reaction	-	Not related	Recovered/ resolved
B (1[redacted] years of age, male)	Present	Absent	Bacterial infection	-	Not related	Recovered/ resolved
			Sepsis/respiratory dysfunction/ decompensation cardiac	Serious	Not related	Recovered/ resolved
			Subarachnoid haemorrhage	Serious	Not related	Recovered/ resolved with sequelae
C ([redacted] years of age, male)	Absent	Present	Recurrent bleeding and haematoma due to a fall	Serious	Not related	Recovered/ resolved
D (1[redacted] years of age, female)	Absent	Unknown	Pyrexia	-	Not related	Unknown
E ([redacted] years of age, male)	Absent	Absent	Pyrexia of 38.5°C	-	Not related	Recovered/ resolved
F ([redacted] years of age, female)	Absent	Present	Headache	-	Not related	Recovered/ resolved
G (2[redacted] years of age, female)	Present	Absent	Deep vein thrombosis	Serious	Related	Not recovered/ resolved
H (2[redacted] years of age, female)	Absent	Present	Nausea/dyspnoea/headache	-	Related	Unknown
I (4[redacted] years of age, male)	Unknown	Present	Rectal haemorrhage	Serious	Not related	Recovered/ resolved

a) Age at the time of receiving eptacog alfa.

7.1.2 Japanese observational study (CTD 5.3.5.4-2: Study F7HAEM-4030, June 2013 to June 2017, reference data)

To collect information on the efficacy and safety of eptacog alfa in Japanese GT patients, a Japanese observational study was conducted based on the instructions imposed when GT was added as an indication for eptacog alfa. Table 5 shows a summary of the results.

Table 5. Summary of the results of the Japanese observational study

Patient	Disease type	Platelet transfusion		Anti-platelet antibodies	Treatment with eptacog alfa					Adverse events
		Prior treatment	Refractoriness		Purpose[a)]	Eptacog alfa administration		Concomitant treatment	Efficacy[b)]	
						No. of times	Mean dose			
J ([redacted] years of age, female)	[redacted]	Treated	Absent	Present	Bleeding	3	82.0 μg/kg/dose	Platelet transfusion	Effective	Not reported
K ([redacted] years of age, male)	[redacted]	Treated	Absent	Absent	Bleeding #1	3	63.0 μg/kg/dose	Other hemostatic treatment than platelet transfusion	Effective	Not reported
					Bleeding #2	2	67.2 μg/kg/dose	Platelet transfusion + other hemostatic treatment	Effective	
					Surgery	1	210.1 μg/kg/dose	Other hemostatic treatment than platelet transfusion	Effective	
L ([redacted] years of age, female)	[redacted]	Untreated	Absent	Absent	Bleeding	2	56.6 μg/kg/dose	None	Effective	Not reported
M ([redacted] years of age, female)	[redacted]	Untreated	Unknown	Absent	Bleeding	6	75.3 μg/kg/dose	Other hemostatic treatment than platelet transfusion	Effective	Not reported

a) Bleeding, bleeding episode; Surgery, hemostatic management of surgery.
b) Treatment of bleeding episodes: Effective (no bleeding for ≥6 hours), partially effective (bleeding reduced but persisting), ineffective (bleeding unchanged or worsened), or unevaluable.
Hemostatic management of surgery: Effective (normal hemostasis), partially effective (mild bleeding tendency), ineffective (excessive bleeding tendency), or unevaluable.

7.2 Other information

7.2.1 Management guidelines

Descriptions of the proposed indications in the representative management guidelines are as follows:

- Management guideline by the United Kingdom Haemophilia Centre Doctors' Organisation (*Br J Haematol*. 2006;135:603-33): When bleeding management with local intervention and anti-fibrinolytic drugs fails, the treatment options are platelet transfusion, recombinant activated human factor VII (rFVIIa), and their combination. For non-life-threatening bleeding, such as nasal bleeding and oral bleeding, for which the site of bleeding can be easily evaluated, if hemostasis is insufficient with local intervention or oral tranexamic acid, rFVIIa can be used in preference to platelet transfusion.
- Guideline by the Gulf Cooperation Council comprised of 6 Persian Gulf countries with a high GT prevalence (*J Appl Hematol*. 2019;10:1-9): For more severe or non-responsive bleeds, rFVIIa can be used as the first line of therapy for bleeding management in GT patients to enable treatment with platelet transfusion.
- Consensus recommendations from the French reference center (*Orphanet J Rare Dis*. 2023;18:171): In the event of refractoriness to platelet transfusions or when platelets are not readily available, rFVIIa can be used for severe bleeding and during surgery.

7.2.2 Published literature

A total of 161 published articles regarding the efficacy and safety of eptacog alfa in GT patients were extracted by a search using terms such as "NovoSeven (including the non-proprietary name, brand name, and "recombinant activated factor VII")," "Glanzmann," "thrombasthenia," "antibody" in BIOSIS Previews, Current Contents Search, Embase, and MEDLINE. Of them, 6 articles contained information on eptacog alfa treatment in GT patients without anti-platelet antibodies or those who are not refractory to platelet transfusions. Table 6 shows the 6 articles. (Last accessed on January 21, 2024)

Table 6. Published articles containing information on eptacog alfa treatment in GT patients

Published literature	Summary
J Thromb Haemost. 2004;2:1096-103	When eptacog alfa was administered to 59 GT patients (29 patients with anti-platelet antibodies and 23 patients with refractoriness to platelet transfusions), eptacog alfa was effective in 29 of 31 surgical procedures and 77 of 103 bleeding episodes (including 8 episodes with recurrence). Serious adverse events for which a causal relationship to eptacog alfa was not ruled out were 1 event each of deep vein thrombosis accompanied by pulmonary embolism and coagulation of one ureter.
Haemophilia. 2010;16:123 (28P11)	In 3 GT patients undergoing tooth extraction (2 patients with anti-platelet antibodies and 1 patient with allergic reaction to platelet transfusions), eptacog alfa and tranexamic acid were administered for hemostasis.
Haemophilia. 2011;17:858-69	During 40 pregnancy events in 35 female GT patients, 13 bleeding episodes after the first delivery and 9 bleeding episodes after a subsequent delivery were reported. For 2 episodes after the first delivery (including 1 episode without anti-platelet antibodies) and 2 episodes after subsequent delivery, eptacog alfa was administered alone or in combination with platelets and other hemostatics.
Haemophilia. 2012;18:49-50	In the case of artificial ankle joint replacement in 1 GT patient without anti-platelet antibodies, eptacog alfa and tranexamic acid were administered before and after surgery in combination with platelet transfusion. The surgery was successful without abnormal bleeding before and after surgery.
Haematologica Polonica. 2015;46:88	In a GT patient without anti-platelet antibodies who had been treated with blood transfusion and eptacog alfa for past bleeding episodes, platelet transfusion, eptacog alfa/tranexamic acid, and endoscopic laser coagulation were used to achieve hemostasis.
EAHAD2023, PO277 (*Haemophilia*. 2023;29)	In 3 of 8 GT patients without anti-platelet antibodies, eptacog alfa was administered periodically for prophylaxis of bleeding.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the efficacy of eptacog alfa in GT patients based on the results of the foreign registry survey and the Japanese observational study:

The overall results of the foreign registry survey [see Section 7.1.1] showed that treatment with eptacog alfa (Table 2) was determined to be effective in 78.7% of the bleeding episodes (262 of 333 episodes). The proportions of episodes in which the treatment was determined to be effective in the population without anti-platelet antibodies (74.2%-84.9%) and the population that was not refractory to platelet transfusions (55.6%-84.9%) were similar to that (72.2%) in the population with anti-platelet antibodies and refractoriness to platelet transfusions, which corresponds to the approved indications. Although some patients also received other concomitant treatments such as platelet transfusion in addition to eptacog alfa, there were no clear differences in the proportion of episodes in which the treatment was determined to be effective among subgroups by concomitant treatment (64.8%-85.7%).

The overall results of hemostatic management of surgery in patients treated with eptacog alfa (Table 3) showed that treatment with eptacog alfa was determined to be effective in 88.1% of the cases (140 of 159 cases). As in the results of the treatment of bleeding episodes, the proportions of cases in which the treatment was determined to be effective in the population without anti-platelet antibodies (66.7%-95.7%) and the population without

refractoriness to platelet transfusions (84.0%-100%) were similar to that (95.0%) in the population with anti-platelet antibodies and refractoriness to platelet transfusions, which corresponds to the approved indications. There were no clear differences in the proportion of cases in which the treatment was determined to be effective among subgroups by concomitant treatment (68.2%-100%).

In the Japanese observational study [see Section 7.1.2], eptacog alfa was administered to 4 GT patients without anti-platelet antibodies or who were not refractory to platelet transfusions for 5 bleeding episodes and for 1 case of hemostatic management of surgery. The treatment was determined to be effective in all of these cases (Table 5).

In view of the above results, as well as descriptions in the management guidelines and treatment experiences reported in published articles, the efficacy of eptacog alfa stated in the present application has been confirmed.

PMDA accepted the applicant's explanation. On the basis of the data submitted, PMDA has concluded that the efficacy of eptacog alfa in both GT patients without anti-platelet alloantibodies and GT patients who are not refractory to platelet transfusions is public knowledge in the fields of medical and pharmaceutical sciences.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.2 Safety

The applicant's explanation about the safety of eptacog alfa in GT patients based on the results of the foreign registry survey and the Japanese observational study:

Table 4 shows the adverse events reported in the foreign registry survey [see Section 7.1.1]. There were no clear differences in the adverse event profiles, including adverse drug reactions listed in the package insert, regardless of the status of anti-platelet antibodies and refractoriness to platelet transfusions, and there are no literature reports suggesting such differences. Additionally, although the safety information collected as post-marketing data from December 1, 2017 to December 31, 2022 included 150 adverse drug reactions (71 serious events and 79 non-serious events) in 52 GT patients, no new safety concerns have been identified. Therefore, events requiring caution during treatment with eptacog alfa in GT patients without anti-platelet alloantibodies and GT patients who are not refractory to platelet transfusions are the same as those for the approved indications, and the safety risk can be managed by continuing the current safety measures.

PMDA accepted the applicant's explanation. On the basis of the data submitted, PMDA has concluded that the safety of eptacog alfa in both GT patients without anti-platelet alloantibodies and GT patients who are not refractory to platelet transfusions is public knowledge in the fields of medical and pharmaceutical sciences, and that the safety measures for its use for the approved indications should be continued.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.3 Clinical positioning, indications, and dosage and administration

PMDA's view:

GT is an autosomal recessive bleeding disorder due to deficient or abnormal fibrinogen receptor GP IIb-IIIa. There is no radical treatment for GT. While mild bleeding can be managed by methods such as local compression and antiplasmins, serious bleeding and surgery require platelet transfusion. According to the relevant website, eptacog alfa is recommended for use in patients with refractoriness to platelet transfusions resulting from development of alloantibodies against platelets or HLA due to repeated platelet transfusion (https://www.shouman.jp/disease/details/09_20_033/, Information Center for Specific Pediatric Chronic Diseases, Japan [last accessed on July 3, 2024]).

However, confirmation of the status of alloantibodies in patients with bleeding symptoms requiring urgent medical intervention is often difficult due to time constraints, and this is a medical issue. There is also a report (*Expert Opin Orphan Drugs*. 2017;5:641-53) that recommends the use of eptacog alfa instead of platelet transfusion for Type I GT patients and female GT patients of reproductive/prepubescent age, because Type I GT patients with severe mutations are considered to have a higher risk of developing anti-GP IIb-IIIa antibodies, i.e., anti-platelet antibodies, and in pregnant women with anti-GP IIb-IIIa antibodies, these antibodies may cross the placenta to cause thrombocytopenia and bleeding in the fetus and newborn.

On the basis of the above background information, the discussions in Sections 7.R.1 and 7.R.2, and the approval status in Europe and the US, eptacog alfa can be used in GT patients who are refractory to platelet transfusions regardless of the status of platelet alloantibodies. In Europe, the use of eptacog alfa is permitted when platelets are not readily available. According to the applicant's explanation, the situation in which platelets are not readily available is defined as a medical situation where it is difficult to obtain platelets and platelets cannot be used for treatment. In general, a medical situation where it is difficult to obtain platelets can occur regardless of the patient's condition. Under such medical conditions, eptacog alfa can be used in GT patients irrespective of the status of refractoriness to platelet transfusions. Accordingly, given that (a) the use of eptacog alfa in GT patients who are not refractory to platelet transfusions is already permitted under specific medical conditions in Europe; (b) the efficacy and safety of eptacog alfa in GT patients who are not refractory to platelet transfusions are considered to be public knowledge in the fields of medical and pharmaceutical sciences, as described in Sections 7.R.1 and 7.R.2; and (c) the use of eptacog alfa is considered in Type I GT patients and female GT patients of reproductive/prepubescent age, even if they are not refractory to platelet transfusions, as described above; a focus should be placed on the appropriateness of administering eptacog alfa to GT patients who are not refractory to platelet transfusions when determining the target population for the use of eptacog alfa in Japan. Based on the above, and in view of the use status of eptacog alfa in the foreign registry survey [see Section 7.1.1], descriptions in the management guidelines [see Section 7.2.1], as well as the fact that the use of eptacog alfa is decided by physicians with adequate knowledge about GT, eptacog alfa can be a treatment option in addition to platelet transfusion for GT patients who are not refractory to platelet transfusions, while also taking account of the characteristics of the patient, such as age, sex, and clinical symptoms, as well as the medical circumstances related to platelet products. In relation to this, the description "past or present refractoriness to platelet transfusions" in the Indications section should be moved to the Precautions

Concerning Indications section, and a precaution regarding the patient population eligible for eptacog alfa treatment should also be provided to inform users that eptacog alfa can be used in GT patients who are not refractory to platelet transfusions or whose status is unknown under certain circumstances, in addition to patients with past or present refractoriness to platelet transfusions. It is unnecessary to make substantial changes to the Dosage and Administration section, because the mean dose of eptacog alfa in the foreign registry survey and the Japanese observational study was generally within the range of the approved dosage.

In view of the above review, PMDA concluded that the current statements on eptacog alfa in the Indications, Precautions Concerning Indications, Dosage and Administration, and Precautions Concerning Dosage and Administration section should be modified as shown below.

Indications

Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with anti-platelet alloantibodies, and with past or present refractoriness to platelet transfusions~~

Precautions Concerning Indications

(Glanzmann's thrombasthenia)

~~The status of anti-platelet alloantibodies should be confirmed by anti-platelet antibody testing, etc.~~

Eptacog alfa should be administered to patients who meet either of the following conditions:

- Patients with past or present refractoriness to platelet transfusions
- Patients who are not refractory to platelet transfusions or whose status is unknown, but for whom platelets are not readily available or platelet transfusion is considered inappropriate

Dosage and Administration

- Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with anti-platelet alloantibodies, and with past or present refractoriness to platelet transfusions~~

  A dose of 80 to 120 μg/kg (4.0-6.0 KIU/kg) should be administered every 1.5 to 2.5 hours until hemostasis is achieved and clinical improvement is observed.

Precautions Concerning Dosage and Administration

~~(Glanzmann's thrombasthenia)~~

~~In patients who are not refractory to platelet transfusions, the first line of therapy for Glanzmann's thrombasthenia is platelet transfusion.~~

(Underline denotes additions to and strikethrough denotes deletions from the current approved information/precautions.)

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.4 Post-marketing investigations

On the basis of the reviews in Sections 7.R.1 and 7.R.2, PMDA has concluded that the efficacy and safety of eptacog alfa for the present application are public knowledge in the fields of medical and pharmaceutical sciences, and no additional pharmacovigilance or risk minimization activities are required.

The above PMDA's conclusion will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

This is an application submitted based on public knowledge in the fields of medical and pharmaceutical sciences in accordance with "Handling of Prescription Drugs for Off-label Use" (No. 4 of the Research and Development Division and PMSB/ELD Notification No. 104 dated February 1, 1999). No data subject to compliance assessment were submitted for the present application.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that the efficacy and safety of eptacog alfa in controlling bleeding tendency in patients with Glanzmann's thrombasthenia are public knowledge in the fields of medical and pharmaceutical sciences.

PMDA has concluded that eptacog alfa may be approved if eptacog alfa is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 7, 2024

Product Submitted for Approval

Brand Name	NovoSeven HI Syringe for I.V. Injection 1 mg, NovoSeven HI Syringe for I.V. Injection 2 mg, NovoSeven HI Syringe for I.V. Injection 5 mg
Non-proprietary Name	Eptacog Alfa (Activated) (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	October 30, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, Safety, Clinical Positioning, Indications, Dosage and Administration, and Post-marketing Investigations

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical positioning, indications, and dosage and administration," and "7.R.4 Post-marketing Investigations" of the Review Report (1).

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and dosage and administration as shown below.

Indications

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX
- Control of bleeding tendency in patients with acquired hemophilia
- Control of bleeding tendency in patients with congenital factor VII deficiency
- Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with past or present refractoriness to platelet transfusions~~

(Strikethrough denotes a deletion from the proposed text.)

Dosage and Administration

Reconstitute eptacog alfa (activated) (genetical recombination) using the entire amount of the provided dedicated reconstitution solution. Administer the reconstituted solution intravenously over 2 to 5 minutes.

- Control of bleeding tendency in patients with congenital hemophilia with inhibitors to coagulation factor VIII or IX

  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate if continued treatment is required. For mild to moderate bleeding, 270 μg/kg (13.5 KIU/kg) may be administered as a single dose.

- Control of bleeding tendency in patients with acquired hemophilia

  The initial dose is 90 μg/kg (4.5 KIU/kg). Thereafter, a dose of 60 to 120 μg/kg (3-6 KIU/kg) should be administered by adjusting the dose according to the type and severity of the bleeding. In the early stage of treatment, eptacog alfa (activated) (genetical recombination) should be administered every 2 to 3 hours until hemostasis is achieved and clinical improvement is observed. Thereafter, the dosing interval should be increased as appropriate while treatment is required.

- Control of bleeding tendency in patients with congenital factor VII deficiency

  A dose of 15 to 30 μg/kg (0.75-1.5 KIU/kg) should be administered every 4 to 6 hours until hemostasis is achieved. The dose may be adjusted according to the type and severity of the bleeding. The dosing interval may also be adjusted as appropriate.

- Control of bleeding tendency in patients with Glanzmann's thrombasthenia ~~with past or present refractoriness to platelet transfusions~~

  A dose of 80 to 120 μg/kg (4.0-6.0 KIU/kg) should be administered every 1.5 to 2.5 hours until hemostasis is achieved and clinical improvement is observed.

(Strikethrough denotes a deletion from the proposed text.)

Appendix

List of Abbreviations

EAHAD2023	16th Annual Congress of European Association for Haemophilia and Allied Disorders 2023
Eptacog alfa	Eptacog alfa (activated) (genetical recombination) Brand name: NovoSeven HI Syringe for I.V. Injection 1 mg, NovoSeven HI Syringe for I.V. Injection 2 mg, NovoSeven HI Syringe for I.V. Injection 5 mg
GP IIb-IIIa	glycoprotein IIb-IIIa
GT	Glanzmann's thrombasthenia
GTR	Glanzmann's thrombasthenia registry
HLA	Human leukocyte antigen
PMDA	Pharmaceuticals and Medical Devices Agency
rFVIIa	recombinant activated human factor VII