EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
EMA/CHMP/800979/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NovoSeven

International non-proprietary name: eptacog alfa (activated)

Procedure No. EMEA/H/C/000074/II/0104

Note

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

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List of abbreviations

FDA	Food and Drug Administration
GP	glycoprotein
GPIIb-IIIa	glycoprotein IIb-IIIa
GT	Glanzmann's thrombasthenia
GTR	Glanzmann's thrombasthenia registry
HLA	human leukocyte antigen
HPA	human platelet antigen
N7	NovoSeven alone
N7OH	NovoSeven + other haemostatic treatment
N7P	NovoSeven + platelets
N7POH	NovoSeven + platelets + other haemostatic treatment
Neg	negative
Pos	positive
RBC	red blood cell
rFVIIa	recombinant activated human factor VII
sBLA	supplemental biologics license application
Unk	unknown
WFH	World Federation of Hemophilia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 9 April 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include patients with Glanzmann's thrombasthenia without antibodies to platelets, or where platelets are not readily available, based on a prospective observational registry and literature references. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in section 4.8 of the SmPC and in Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Not applicable, as the product is not protected by a Supplementary Protection Certificate (SPC) or a patent that qualifies for a SPC.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Nithyanandan Nagercoil

Timetable	**Actual dates**
Submission date	9 April 2018
Start of procedure:	28 April 2018

Timetable	Actual dates
CHMP Co-Rapporteur's preliminary assessment report circulated on:	20 June 2018
CHMP Rapporteur's preliminary assessment report circulated on:	26 June 2018
Joint CHMP Rapporteurs updated assessment report circulated on:	20 July 2018
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 July 2018
MAH's responses submitted to the CHMP on:	14 September 2018
PRAC Rapporteur's preliminary assessment report circulated on:	25 September 2018
PRAC RMP advice and assessment overview adopted by PRAC	4 October 2018
Joint CHMP Rapporteurs preliminary assessment report on the MAH's responses circulated on:	5 October 2018
Updated Joint CHMP Rapporteurs preliminary assessment report on the MAH's responses circulated on:	12 October 2018
CHMP Opinion:	18 October 2018

2. Scientific discussion

2.1. Introduction

NovoSeven is indicated for 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 congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
- in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- in patients with acquired haemophilia
- in patients with congenital FVII deficiency
- in patients with Glanzmann's thrombasthenia (GT) with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions

The recommended dose regimen in GT is 90 µg (ranging from 80 to 120 µg) per kg body weight at intervals of 2 hours (ranging from 1.5 to 2.5 hours). At least 3 doses should be administered to secure effective haemostasis.

Purpose of this variation application

The MAH applies to extend use of Novoseven in patients with GT to:

- patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, with or without antibodies to platelets, or where platelets are not readily available.

Brief regulatory history

NovoSeven (rFVIIa) was first granted marketing authorisation in the EU in February 1996 for the indications in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX and in acquired haemophilia. Approval for the above mentioned GT and FVII deficiency indications was granted

in January 2004. In the variation procedure for the indication in GT, the MAH had applied for approval for the following indication:

> Treatment of bleeding episodes and/or prevention of bleeding in connection with invasive/ diagnostic procedures and/or surgery in patients with GT with antibodies to GPIIb/IIIa and/or HLA, or with past or present refractoriness to platelet transfusions or in circumstances with inadequate access to platelet concentrates.

EMA noted that *"platelet transfusion is the current standard treatment of GT when local measures or antifibrinolytic drugs fail to stop bleeding or during invasive/surgical bleeding. Even patients with anti-GPIIb/IIIa and/or anti-HLA antibodies are not per definition refractory to platelets",* therefore the current GT indication was approved.

Glanzmann's thrombasthenia (GT)

GT is a rare (prevalence estimated ~ 1/1,000,000 in Western populations) congenital autosomal recessive bleeding disorder caused by deficiency or abnormality of the platelet membrane glycoprotein IIb-IIIa (GPIIb-IIIa), a fibrinogen receptor. On activated platelets, the GPIIb-IIIa complex is involved in platelet aggregation mediated by fibrinogen binding to this complex.

In Type I GT there are less than 5% of normal GPIIb-IIIa levels and in Type II these are 5−20% of normal. In variant-type the level of GPIIb-IIIa is above 20% with dysfunctional proteins or the level is not defined. Bleeding in GT may be mild to severe.

Women with GT are particularly disadvantaged since they in addition to the other bleeding symptoms also can have excessive bleeding during menstruation, pregnancy and childbirth.

Management of GT

As the bleeding tendency and severity varies in patients with GT, the treatment demands vary considerably.

Mild and moderate bleeding episodes often can be controlled by conservative methods such as local compression, local haemostatic agents (fibrin glue) and anti-fibrinolytic drugs. However, when such treatment fails, the treatment approach is transfusion of platelets.
Platelet transfusion is the standard therapy to control severe bleeding episodes and to prepare patients for surgical interventions. Large amounts of platelets may be required.

In GT, refractoriness to platelet transfusion can be considered when platelet transfusions are clinically ineffective in achieving haemostasis e.g. due to infection, bleeding, splenomegaly or medication. Immune causes of refractoriness include allo-immunisation to human leucocyte antigen (HLA) and/or human platelet antigen (HPA) due e.g. most often to prior exposure from transfusion, pregnancy or transplantation.

Mechanism of action of rFVIIa in GT

Local enhancement of thrombin generation, mediated by rFVIIa, is able to increase adhesion of GPIIb/GPIIIa-deficient platelets. Enhancement of adhesion does not result in a stable platelet plug, but provides an increase of pro-coagulant surface at the site of injury, thus facilitating a further enhancement of thrombin generation and subsequent fibrin formation. Activated GT platelets cannot bind fibrinogen, as they lack the fibrinogen receptor (GPIIb/IIIa). However, binding of fibrin/polymeric fibrin to an as yet unidentified platelet surface receptor can mediate aggregation of the GT platelets at the wound site. This fibrin-mediated GT platelet aggregation was partially dependent on binding of thrombin to GPIb. Fibrin appeared an active participant in mediating platelet aggregation partly in a receptor-mediated manner as opposed to being passively trapped, since aggregation was less efficient if viable platelets were replaced by fixed platelets.

Glanzmann's Thrombasthenia Registry

The condition for approving the variation application was the commitment by Novo Nordisk A/S to establish a post-marketing efficacy and safety data collection system collecting specified clinical data from patients with GT treated with rFVIIa. The focus should be on the administered dose regimens, efficacy and safety (especially the occurrence of thromboembolic complications in relation to concomitant use of anti-fibrinolytics).

Reporting from the GTR

The GTR was initiated in 2004 and after initial delays in order to optimise its operation; five interim reports were submitted by Novo Nordisk. These reports have been assessed by the Rapporteur, and assessment reports have been issued in October 2007, December 2008, May 2009, July 2010 and September 2011 respectively. The commitment was fulfilled with the submission of the 5th GTR report to the EMA in February 2011. However, the GTR was continued until its closure in December 2011 and a final GTR report version 6.0 was prepared (report date 23 August 2013).

Expert panel meetings – statement

Several expert panel meetings were conducted during the registry. The expert panel meeting in November 2010 resulted in a statement from the expert panel regarding the following points:

- Definition of platelet refractoriness in GT
- Concomitant use of rFVIIa and platelets – are the patients refractory?
- GT indication: the relevance of both platelet refractoriness and platelet antibodies as prerequisite to use rFVIIa
- Re-bleeding/post-surgical bleeding – definitions

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Applicant states that since the Glanzmann Thrombasthenia Registry (referred to as GTR) (F7HAEM-3521 (F7GLANZ)) was based on clinical data collected from general clinical practice; the patient's records met the standards of the participating sites. Good Clinical Practice (GCP) required for clinical trials could not be expected to be met. However, to ensure a certain data quality, randomly chosen sites (corresponding to about 10% to 20% of the reported cases) and sites where Novo Nordisk identified a need were monitored. All serious adverse events were to be monitored and data validated by Novo Nordisk A/S.

Data Sources

To support this extension of the indication, data from the GTR, (a post-marketing, observational, multinational web-based registry), literature review and adverse events reported spontaneously to Novo Nordisk are used. An overview of data source is provided in Table 1

Source data are included in the dossier as follows:

- GTR.
- Published literature.
- Novo Nordisk safety database with spontaneous reports, solicited reports from post observational studies/registries and cases published in the literature.

Published literature was searched for the period 01 January 1999 to 01 December 2017 and included only medical literature published in English. Overall, there were 143 literature references identified during the search, 14 of which contained sufficient predefined assessments of efficacy to warrant inclusion.

Table 1 Overview of efficacy and safety data in patients with Glanzmann's thrombasthenia

Data source	Design	No of patients/cases	Treatments
GTR[a]	A post-marketing, observational, multinational web-based registry designed to collect and evaluate the efficacy and safety of NovoSeven® (with or without concomitant haemostatic medication) in severe bleeding episodes requiring systemic hemostatic therapy and in prevention of bleeding during surgery in patients with GT.	133 patients[d]	Dosed according to local treatment practice
Published Literature/Case Reports[b]	Multiple-database search covering January 1999 to December 2017.	30 patients	Dosed according to local treatment practice
Novo Nordisk safety surveillance database (ARGUS) with spontaneous reports, solicited reports from post-authorisation studies and registries, and reports published in the literature[c]	Safety data from marketed use collected in the Novo Nordisk safety database. Data include spontaneous reports, adverse drug reactions from published literature and solicited reports from ongoing registries.	53 cases[e]	

[a] Data source used for efficacy and safety evaluation

[b] Data source used for efficacy evaluation

[c] Data source used for safety evaluation

[d] Only data from patients who have been treated with NovoSeven® either alone or in combination with other haemostatic treatment and/or platelets are included.

[e] The total number of cases include 17 cases from the literature and 1 case from the GTR

Abbreviations: GT = Glanzmann's thrombasthenia; GTR = Glanzmann's thrombasthenia registry

2.4. Clinical efficacy

2.4.1. Main study

F7GLANZ

Treatment of Glanzmann's Thrombasthenia: A prospective observational registry

Methods

Study participants

Inclusion criteria:

- Patients (males and females of any age) with congenital GT defined as patients with lifelong bleeding tendency characterised by impaired or absent platelet aggregation, impaired clot

retraction and prolonged bleeding time or prolonged platelet function analyser closure time. The patients have normal platelet counts and platelet morphology. Optional diagnosis criteria are quantitative or qualitative evaluation of GPIIb/IIIa receptors including flow cytometry and identification of gene defects.

- Signed informed consent by the patient or next of kin or legally acceptable representative to collect data on treatment of a given bleeding episode or surgical event as specified in the protocol. Consent must also be obtained from the patient as soon as he or she is able to do so. Informed consent must be obtained before entry of data into the registry.

Both retrospective (as of 2004) and prospective cases were entered into the registry.

Exclusion criteria:

Patients with acquired thrombasthenic states caused by autoimmune disorders (acute or chronic) or drugs were to be excluded from entering the registry.

Treatments

The registry collected data from patients with GT treated with rFVIIa. The registry also collected data from patients with GT treated with other systemic haemostatic treatments (with or without antifibrinolytic drugs or other agents) used in the clinics.

All patients in the GTR were treated in accordance with local treatment practices and patients exposed to rFVIIa were treated according to the EU package insert for Novoseven or based on medical judgement by the primary physician in an open-label manner. No drugs were supplied for this registry.

For comparison, information about the efficacy of other haemostatic treatments in patients with GT is also included in the registry.

Concomitant therapy

For the rFVIIa treated patients, any other haemostatic medication and non-haemostatic treatment at the time of a bleeding episode or surgical event was registered as concomitant medication.

Objectives

The objectives of the registry were:

- To evaluate the efficacy and safety of rFVIIa during bleeding episodes and for the prevention of bleeding during invasive procedures/surgery in patients with GT with past or present refractoriness to platelet transfusions. Attention was directed towards complications related to thromboembolic events and concomitant medications, especially anti-fibrinolytics.
- To describe the outcome of bleeding episodes and surgeries requiring systemic haemostatic treatment (with or without antifibrinolytic drugs or other agents) in patients with GT in real-life clinical settings.

Outcomes/endpoints

Efficacy of treatments given for a bleeding episode or for surgery was evaluated.

Efficacy variables recorded in the treatment of bleeding episodes

- Cause of bleed (spontaneous, traumatic and other [non-surgical])

- Type of bleeding (see Appendix 16.1.2 of the GTR report, case report form, for further details regarding type of bleeding)
- Onset of symptoms (date and time)
- Patients treated with rFVIIa (yes/no)
- Haemostatic treatment prior to rFVIIa administration (date, time and type)
- Recombinant FVIIa administration (date, time and dose for all doses given)
- Other haemostatic treatments concomitant to rFVIIa (type and dose)
- Other concomitant medications (yes/no, type and date)
- Concomitant illness (yes/no, type and date)
- Post-infusion complications/adverse events (yes/no)
- Efficacy evaluation

The rFVIIa administrations could be entered in the registry with dose, date and time for a maximum of 10 administrations. All administrations above 10 could only be entered as the total dose given for all additional administrations.

Efficacy evaluation of bleeding episodes

An overall efficacy evaluation was performed for patients treated on-demand for a bleeding episode by the end of the treatment according to the following scale and definitions presented in Table 2.

The time between the first rFVIIa dose administration and performance of the overall efficacy evaluation was assessed and entered into the GTR.

Table 2 Efficacy evaluation scale and definition during bleeding episodes

Scale	Definition
Effective[a]	Bleeding stopped/haemostasis achieved for 6 hours or more
Partially effective[b]	Bleeding had decreased substantially but continued
Ineffective[b]	Bleeding was unchanged or worsened
Not possible to evaluate[c]	Not applicable

a) If the treatment is considered effective, it should be entered if bleeding stopped in: 1) <6 hours, 2) 6–24 hours or 3) >24 hours after first dose.
b) For treatment outcomes evaluated as partially effective or ineffective, alternative treatment is to be specified.
c) For treatment outcomes not possible to evaluate, a reason is to be specified.

If the treatment was considered partially effective or ineffective, the treatment used instead was specified:

1. Treatment stopped and alternative treatment started

The treatment was evaluated as partially effective or ineffective (as appropriate) and the effect of the alternative treatment was entered.

2. Treatment continued and additional treatment added

The combined effect was evaluated using the standard evaluation scheme. Additional treatment should be entered in 'Concomitant treatment'. A note on combined effect of treatment and concomitant treatment could have been entered.

Re-bleeding

Re-bleeding was defined as a bleeding starting more than 6 hours, but less than 48 hours after arrest of previous bleed.

In case of re-bleeding, the location, bleeding intensity, days after treatment start and time after last treatment dose were assessed and entered into the GTR.

Prophylactic treatment during surgery

If the patient was treated prophylactically before and during surgery (including invasive or dental procedures), the following information was recorded:

- Type of surgery (elective or emergency)
- Indication for surgery and type of surgery
- Date and time of surgery (start and stop time)
- Treatment prior to, during and after surgery
- Platelet transfusion (type and dose)
- rFVIIa administration (date, time and dose for all doses given)
- Anti-fibrinolytics (type)
- Other haemostatic treatments (type)
- Heparin prophylaxis (yes/no)
- Other concomitant medications (other than haemostatics) (yes/no)
- Concomitant illness (yes/no)
- Complications/adverse events (yes/no)
- Haemostatic evaluation

The rFVIIa administrations could be entered in the registry with dose, date and time for a maximum of 20 administrations prior to, during and after surgery (thus a maximum of 60 rFVIIa administrations could be entered). All administrations above 20 could only be entered as the total dose given for all additional administrations (prior to, during and after surgery).

Haemostatic evaluation of surgery

Similarly, an overall haemostatic evaluation was performed for patients treated in relation to surgery according to the scale and definitions presented in Table 3.

Table 3 Overall haemostatic evaluation scale and definition during surgery

Scale	Definition
Effective	Normal haemostasis
Partially effective	Mild bleeding tendency
Ineffective[a]	Excessive bleeding tendency
Not possible to evaluate[b]	Not applicable

a) For treatment outcomes evaluated as ineffective, alternative treatment is to be specified.
b) For treatment outcomes not possible to evaluate a reason is to be specified.

The following results were reported for patients treated during surgery (including invasive or dental procedures):

- Haemoglobin level prior to and 24 hours after surgery (g/dL or mmol/L)
- Units of RBC given during surgery, within 24 hours after surgery and from 24 hours after surgery to time of hospital discharge (units)
- Time spent in hospital post-operation (total days)

Safety variables

The following safety variables were recorded:

- Adverse events
- Clinical laboratory adverse events
- Serious adverse events
- Non-serious adverse events
- Medical events of special interest which included thromboembolic events, immunogenicity, medication errors (wrong drug administration or wrong route of administration) and suspected transmission of an infectious agent via the product.

Reporting of adverse events

All adverse events either observed by the treating physician or reported spontaneously by the patient were collected from the first administration of pharmaceutical products and until 24 hours after the last dose and subsequently entered into the GTR. The physician was required to report serious adverse events and medical events of special interest involving rFVIIa to Novo Nordisk A/S within 24 hours of obtaining knowledge about the event. The physician informed regulatory authorities and independent ethics committee/institutional review board (IEC/IRB) of serious adverse events not related to rFVIIa treatment in accordance with local requirements.

Clinical laboratory tests

Assessments of prothrombin time, platelet count and fibrinogen were optional. If the assessments were performed, values obtained at the time of administration and 2 hours after the administration of rFVIIa were to be entered into the GTR. If more doses of rFVIIa were given, laboratory values obtained at the same time points were to be entered into the GTR.

Sample size

According to the protocol, sample size was not calculated prospectively as data collection was to run until adequate efficacy and safety information is accumulated or for a maximum of six years. All patients in the registry were included in the GTR report.

Data handling

The patients were assigned randomly generated numbers. No personal information was entered in the registry. All data management and data validation were performed by Novo Nordisk A/S.

Cases were considered complete if: they contained sufficient medical information to allow for a medical evaluation of the event; all data points on the query list were filled in and the case did not contain internal conflicting information. The data in the GTR eCRF have systematically been reviewed by an internal medical haematologist analysing all cases in the GTR.

Queries were sent out to sites in case of missing, inconsistent or ambiguous information. Answers to queries were entered in the eCRF. Subsequently these answers have been cleared by medical check for validity. After completion of checks for each case, the case was locked, thus preventing further changes by centres or data managers.

Randomisation

Not applicable.

Blinding (masking)

This trial is an observational study without any blinding issues.

Statistical methods

Analysis sets

In the GTR report no analysis sets were defined, but all data from all subjects/admissions are presented.

This did not compromise the protocol, since all efficacy and safety data are presented for all subjects/admissions where data are available.

Descriptive statistics

All evaluations were summarised. Summary tables for numerical variables included mean, standard deviation, median, min. and max. Categorical variables were summarised as numbers and percentages. Statistical analyses were to be performed where applicable.

Efficacy variables and analyses

Efficacy evaluations were summarised as number of subjects, number of admissions, number and percentage of admissions with each efficacy evaluation according to the SAP .

Safety variables and analyses

- Frequency of adverse events and serious adverse events during and after administration of rFVIIa either on-demand or prophylactically
- Changes in laboratory parameters (prothrombin time, platelet count, fibrinogen) if available

Protocol amendments

Protocol version 1.0 was dated 21 December 2004.

Only amendment points considered to be relevant are mentioned here.

Protocol Version 2.0, dated 20 July 2005

Adding the possibility for the physician to enter data on a paper case report form versus electronic entries.

This increased the number of participating sites by allowing investigators who did not have internet access to enter data on a paper CRF.

Protocol Version 3.0, dated 10 January 2008

- Planned inclusion of first patient changed from Q1 2005 to Q1 2007.
- Planned recruitment period changed from 2 - 6 years to 2 - 4 years.
- Cases generated from 2004 may be entered into the registry retrospectively.

Protocol Version 4.0, dated 11 February 2008

Reporting frequency changed to twice a year.

A second substantial amendment was prepared in which planned changes to protocol version 4.0 included:

- a clarification of the timelines of the study (planned data capture period was to be changed to 2-6 years),
- a clarification of re-bleeding for bleeding episodes and
- the voluntary inclusion of DNA analysis for diagnosis of GT.

In most of the countries involved in the registry and as per local regulations, the DNA test would have implied the study to be changed from 'observational' to 'interventional'. Thus, this amendment was not accepted.

Queries sent to all sites participating in the registry revealed that in most cases this diagnosis is not performed by analysis of genetic defect/mutation.

Sites were informed of the clarification of re-bleeding for bleeding episodes and also of the definition of post-surgical bleeding.

Results

Participant flow

There were a total of 218 patients with GT with 1073 admissions included in the registry.

Recruitment

Patients were recruited to the registry at 45 sites from 15 countries worldwide (one site in the USA, one in Pakistan, 6 in Algeria and the rest in 13 countries in Europe). The GTR was initiated on 31 December 2004 (first entry of data was 10 May 2007). Since admissions could be entered retrospectively, the first admission date is 1January 2004. The GTR was closed on 16 December 2011.

Seven treatment groups were defined as shown in **Table 4**.

Table 4 Treatment groups

	Treatment group*	Definition**
Treated with rFVIIa	N7	rFVIIa only
	N7POH	rFVIIa + platelets + other haemostatic treatment
	N7OH	rFVIIa + other haemostatic treatment (no platelets)
	N7P	rFVIIa + platelets only
Treated with other treatments than rFVIIa	POH	Platelets + other haemostatic treatment
	OH	Other haemostatic treatment only
	P	Platelets only

* For surgery admissions, in the listings, 'S' has been included in the name of the treatment groups (e.g., S N7OH).
** For surgery admissions, the treatment received is either *prior* and/or *during* and/or *after* surgery.

Some patients and admissions were not included in the registry due to various reasons:

- Admission date is prior to 01-01-2004 (n=19 admissions).
- Not accepted as case was entered into the database after the cut-off date of 20-10-2011 (n=9 admissions).
- No systemic, haemostatic treatment given (n=18 admissions).
- Deleted by investigator, no reason provided (n=5 admissions).

Deleted by investigator, as information on treatment regimen was not available. (n=1 admission).

Conduct of the study

Protocol deviations

All patients included in the registry met the inclusion criteria, and none met the exclusion criteria.

There were no procedural deviations as patients were treated according to general local practice with no specific procedures requested.

Baseline data

All Patients in the GTR

Patient demographics in the GTR are summarised in **Table 5**.

Of the 218 patients in the registry 127 patients (58%) were females. The mean age was 20.4 years (range 0-80 years).

In (34%) of patients the diagnosis was type I GT, 10% had Type 2 GT and disease type was unknown.

In 114 (52%) patients (in 2 patients the information was missing). The genetic defect was specified in 23 patients.

Table 5 Demographics and other baseline characteristics of all patients in the GTR

	Registered	N7 treated
Total number of pt. in registry	218	133
Age at first Admission (Years)		
n	216	131
Mean (Std)	20.4 (17)	24.1 (18)
Range	0 – 80	0 – 80
Age at first Admission, N (%)		
< 12	87 (40)	41 (31)
12-17	19 (9)	16 (12)
>= 18	110 (50)	74 (56)
No Age	2 (1)	2 (2)
Sex, N (%)		
Female	127 (58)	75 (56)
Male	90 (41)	58 (44)
Unknown	1 (0)	0 (0)
Ethnic Origin, N (%)		
African	10 (5)	6 (5)
Asian	51 (23)	14 (11)
Caucasian	112 (51)	72 (54)
Middle East	1 (0)	1 (1)
Other	10 (5)	10 (8)
Unknown	34 (16)	30 (23)
Disease Type, N (%)		
Type 1	74 (34)	62 (47)
Type 2	22 (10)	13 (10)
Variant	8 (4)	3 (2)
Unknown	114 (52)	55 (41)

Cross-reference: From EOT Table 14.2.3.

Patients treated with Novoseven

Demographics for the GTR population treated with NovoSeven are shown in **Table 6**.

Of the 133 patients treated with NovoSeven, 75 (56%) were female. The mean age was 24.1 years (range: 0−80 years). The populations included a substantial number of young children (31% aged <12 years) and adults (56% aged ≥18 years). The majority of patients were Caucasian (54%).

The majority of patients (47%) had type I GT and in 41% of patients disease type was unknown.

Table 6 Demographics and patient history for patients treated with NovoSeven

		N7	N7POH	N7OH	N7P	All[a]
Number of patients, N(%)		62 (100)	45 (100)	85 (100)	11 (100)	133 (100)
Age at first Adm. (Years)	n	61	45	84	11	131
	Mean (Std)	23.3 (16)	20.8 (19)	22.9 (17)	18.4 (17)	24.1 (18)
	Min ; Max	1 ; 64	0 ; 80	1 ; 80	2 ; 64	0 ; 80
Age at first Adm., N(%)	< 12	17 (27)	20 (44)	26 (31)	5 (45)	41 (31)
	12-17	7 (11)	4 (9)	10 (12)	1 (9)	16 (12)
	>= 18	37 (60)	21 (47)	48 (56)	5 (45)	74 (56)
	No Age	1 (2)	-	1 (1)	-	2 (2)
Sex, N(%)	Female	36 (58)	24 (53)	48 (56)	8 (73)	75 (56)
	Male	26 (42)	21 (47)	37 (44)	3 (27)	58 (44)
Ethnic Origin, N(%)	African	4 (6)	1 (2)	3 (4)	-	6 (5)
	Asian	4 (6)	5 (11)	9 (11)	1 (9)	14 (11)
	Caucasian	30 (48)	29 (64)	45 (53)	9 (82)	72 (54)
	Middle East	1 (2)	1 (2)	1 (1)	-	1 (1)
	Other	4 (6)	3 (7)	3 (4)	1 (9)	10 (8)
	Unknown	19 (31)	6 (13)	24 (28)	-	30 (23)
Disease Type[b], N(%)	Type I	30 (48)	18 (40)	49 (58)	3 (27)	62 (47)
	Type II	7 (11)	4 (9)	7 (8)	2 (18)	13 (10)
	Variant	2 (3)	1 (2)	2 (2)	-	3 (2)
	Unknown	23 (37)	22 (49)	27 (32)	6 (55)	55 (41)

The symbol dash (-) indicates missing values.

[a]Patients who changed therapy during the study period or had both surgeries and bleedings, have been counted in several groups, therefore the number of patients in each group does not sum up to the total.

[b]The disease is classified based on the level of platelet GPIIb-IIIa complexes present: type I (less than 5% of normal GPIIb-IIIa levels), type II (5-20% of normal GPIIb-IIIa levels), variant-type (the level of GPIIb-IIIa is above 20%; however, the proteins are dysfunctional) or the level is not defined.

Abbreviations: Adm = admission; N = number of patients; N7 = NovoSeven® alone; N7OH = NovoSeven® + other haemostatic treatment; N7P = NovoSeven® + platelets; N7POH = NovoSeven® + platelets + other haemostatic treatment; Std = standard deviation

Numbers analysed

Patients treated with Novoseven

133 patients (492 admissions) were treated with NovoSeven with or without other haemostatic treatment.

- 94 patients with 333 admissions for bleeding episodes and
- 77 patients with 159 admissions for surgical procedures

NovoSeven was given alone or in combination with platelets and/or another haemostatic treatment resulting in the following 4 treatment groups and numbers who received those treatments for an admission (**Table 7**).

Table 7 Novoseven treatment groups

Treatment group	Definition	

N7	rFVIIa only	62
N7POH	rFVIIa + platelets + other haemostatic treatment	45
N7OH	rFVIIa + other haemostatic treatment (no platelets)	85
N7P	Platelets only	11

Note that patients could have both bleeding episodes and surgeries registered, and that the treatment could vary between the admissions; thus, the sum of the number of patients in each treatment group does not always add up to the total number of patients in the presented tables, but may be a higher number (see also red boxed information in Table 8).

Table 8 Patient and admission disposition by treatment group

	Tx group	Bleeding episodes		Surgeries		Total	
		No. of patients	No. of admissions	No. of patients	No. of admissions	No. of patients	No. of admissions
All	**Total**	**184**	**870**	**96**	**204**	**218**	**1073**
Treated with rFVIIa	Total	94	333	77	159	133	492
	N7	38	155	35	62	62	217
	N7POH	34	54	19	22	45	76
	N7OH	55	110	42	71	85	181
	N7P	10	14	4	4	11	18
Treated with other treatments than rFVIIa	Total	139	537	36	45	152	581
	POH	77	213	19	23	86	235
	OH	85	223	10	12	88	235
	P	42	101	10	10	49	111

Note: One patient could have both bleeding episodes and surgeries registered, and the treatment could vary between the admissions; thus the sum of the number of *patients* in each category does not always add up to the total number of patients in the registry, but may be more. Four admissions with only adverse events are not included in this table, and 9 admissions have been excluded from the summaries as they constitute 2 bleedings and not 9, these admissions are in the listings and are described separately in this report (see Section 9.2.1).

Abbreviations: Tx = treatment; N7 = rFVIIa; OH = other haemostatic treatment; P = platelets.

Outcomes and estimation

Definition of refractoriness

In GT, refractoriness to platelet transfusion can be considered when platelet transfusions are clinically ineffective in achieving haemostasis.

In the GTR, past or present refractoriness to platelets was defined clinically as:

- Persistence of bleeding despite an adequate amount of platelet infusions, or
- Re-bleeding within 24 hours despite an adequate amount of platelet infusions, or
- Bleeding during surgery despite an adequate amount of platelet infusions.

An 'adequate amount' was determined by the clinician.

Platelet refractoriness and antibodies

Data presented from the GTR in relation to refractoriness and antibody status are defined per patient as:

- Positive (POS): at least one positive answer at any admission.
- Negative (NEG): no positive answers, but at least one negative.
- Unknown (UNK): only unknown or missing answers.

It can be recalled that 133 patients in the GTR were treated with NovoSeven (**Table 9** and **Table 10**).

Table 9 Refractoriness to platelets and presence of antibodies

	Total registered	N7 treated
Antibodies, N (%)		
Yes	65 (30)	60 (45)
No	137 (63)	65 (49)
Unknown	16 (7)	8 (6)
GPIIa/IIIb antibodies, N (%)		
Yes	47 (22)	46 (35)
No	6 (3)	5 (4)
Unknown	7 (3)	5 (4)
Missing	5 (2)	4 (3)
HLA antibodies, N (%)		
Yes	21 (10)	19 (14)
No	31 (14)	31 (23)
Unknown	7 (3)	5 (4)
Missing	6 (3)	5 (4)
Other antibodies, N (%)		
Yes	16 (7)	15 (11)
No	18 (8)	18 (14)
Unknown	9 (4)	7 (5)
Missing	22 (10)	20 (15)
Refractoriness, N (%)		
Yes	34 (16)	31 (23)
No	129 (59)	63 (47)
Unknown	49 (22)	34 (26)
Missing	6 (3)	5 (4)
Refractoriness and any antibodies, N (%)	24 (11)	22 (17)
GPIIa/IIIb antibodies, N (%)		
Yes	16 (7)	16 (12)
No	2 (1)	2 (2)
Unknown	5 (2)	3 (2)
Missing	1 (0)	1 (1)
HLA antibodies, N (%)		
Yes	6 (3)	6 (5)
No	10 (5)	10 (8)
Unknown	5 (2)	3 (2)
Missing	3 (1)	3 (2)
Other antibodies, N (%)		
Yes	4 (2)	4 (3)
No	6 (3)	6 (5)

Primarily, results for the following 3 categories are described:

- (NEG/NEG): without refractoriness and antibodies to platelets (37/133 [*27.8*%] 196 admissions)

- (POS/POS): with refractoriness and antibodies to platelets (22/133 [*16.5*%]; 76 admissions)
- (POS/NEG): with refractoriness but without antibodies to platelets (8/133 [*6.0*%] 43 admissions)

The proportion of Novoseven treated patients without antibodies to platelets (irrespective of refractoriness status) (49% [65 of 133 patients], was similar to the proportion of patients with antibodies to platelets (45% [60 of 133 patients]) **Table 9** and **Table 10**.

The proportion of Novoseven treated patients without refractoriness to platelets (irrespective of antibody status) was 47% (63 of 133 patients) compared to with refractoriness to platelets 23% (31 of patients **Table 9 Table 10**.

Further details of numbers of patients and admissions according to possible combinations of refractoriness and antibody status by treatment group are given in Table 10.

A similar pattern was seen for bleeding episodes and surgery.

Table 10 Refractory and antibody categories by NovoSeven treatment

	N7		N7POH		N7OH		N7P		All[a]	
	Pt.	(%) Adm.	Pt.	(%) Adm.	Pt.	(%) Adm.	Pt.	(%) Adm.	Pt.	(%) Adm.
All patients	62	(100.0) 217	45	(100.0) 76	85	(100.0) 181	11	(100.0) 18	133	(100.0) 492
Refract POS / AB POS	14	(22.6) 31	6	(13.3) 10	14	(16.5) 34	1	(9.1) 1	22	(16.5) 76
Refract POS / AB NEG	4	(6.5) 12	4	(8.9) 8	5	(5.9) 21	1	(9.1) 2	8	(6.0) 43
Refract POS / AB UNK	1	(1.6) 4	1	(2.2) 1		-	1	(9.1) 2	1	(0.8) 7
Refract NEG / AB POS	6	(9.7) 12	7	(15.6) 18	17	(20.0) 42		-	21	(15.8) 72
Refract NEG / AB NEG	18	(29.0) 125	15	(33.3) 24	20	(23.5) 38	5	(45.5) 9	37	(27.8) 196
Refract NEG / AB UNK	1	(1.6) 1	4	(8.9) 4	3	(3.5) 4	1	(9.1) 1	5	(3.8) 10
Refract UNK / AB POS	7	(11.3) 12	6	(13.3) 8	11	(12.9) 14		-	17	(12.8) 34
Refract UNK / AB NEG	11	(17.7) 20	2	(4.4) 3	13	(15.3) 24	2	(18.2) 3	20	(15.0) 50
Refract UNK / AB UNK		-		-	2	(2.4) 4		-	2	(1.5) 4

The symbol dash (-) indicates missing values.

[a]Patients who changed therapy during the study period or had both surgeries and bleedings, have been counted in several groups, therefore the number of patients in each group does not sum up to the total.

With regard to treatment, the overall pattern in refractoriness and antibody status was similar for bleeding episodes and surgery. Further, for both bleeding episodes and surgery, the proportion of patients within each refractoriness and antibody category, was comparable between the treatment groups; however, the number of patients in some of the categories was rather small.

Platelet refractoriness and antibodies by age

Overall, the pattern in relation to refractoriness and antibody status was similar for the 3 age groups and in line with the overall results in all patients. The number of patients in the age group 12−17 years was low (19 patients) compared to the age groups <12 years and ≥18 years (41 and 77 patients, respectively **Table 11**).

Generally, a similar pattern in refractoriness and antibody status was seen for bleeding episodes and surgery and in line with the overall results in all patients.

Table 11 Refractory and antibody categories by age

	<12 years Pt. (%)	<12 years Adm.	12-17 years Pt. (%)	12-17 years Adm.	≥18 years Pt. (%)	≥18 years Adm.	No age Pt. (%)	No age Adm.	All[a] Pt. (%)	All[a] Adm.
All patients	41 (100.0)	226	19 (100.0)	41	77 (100.0)	223	2 (100.0)	2	133 (100.0)	492
Refract POS / AB POS	5 (12.2)	23	1 (5.3)	1	17 (22.1)	52	-		22 (16.5)	76
Refract POS / AB NEG	2 (4.9)	22	1 (5.3)	1	6 (7.8)	20	-		8 (6.0)	43
Refract POS / AB UNK	-		-		1 (1.3)	7	-		1 (0.8)	7
Refract NEG / AB POS	6 (14.6)	29	3 (15.8)	11	12 (15.6)	32	-		21 (15.8)	72
Refract NEG / AB NEG	19 (46.3)	132	4 (21.1)	13	14 (18.2)	50	1 (50.0)	1	37 (27.8)	196
Refract NEG / AB UNK	-		4 (21.1)	8	1 (1.3)	2	-		5 (3.8)	10
Refract UNK / AB POS	2 (4.9)	3	-		15 (19.5)	31	-		17 (12.8)	34
Refract UNK / AB NEG	6 (14.6)	14	5 (26.3)	6	11 (14.3)	29	1 (50.0)	1	20 (15.0)	50
Refract UNK / AB UNK	1 (2.4)	3	1 (5.3)	1	-		-		2 (1.5)	4

The symbol dash (-) indicates missing values.

[a]Patients who changed therapy during the study period or had both surgeries and bleedings, have been counted in several groups, therefore the number of patients in each group does not sum up to the total.

Dosing and efficacy – bleeding episodes

Dosing in bleeding episodes

Though there was large variation, the median dose per infusion of NovoSeven in all patients (90 µg/kg) was in line with the recommended and approved dose regimen in GT; that being 90 µg/kg (range 80-120 µg/kg) at intervals of 2 hours (1.5–2.5 hours). The median dose was similar for all 4 treatment groups (90 µg/kg) **Table 12**. In **Table 13** the dose according to bleed severity is given.

Table 12 Dosing in bleeding episodes treated with NovoSeven – by treatment

Treatment group	Total no. adm	Total no. doses*	No. doses* per adm Median (Range)	Dose per infusion (µg/kg) Median (Range)	Total dose per adm (µg/kg) Median (Range)	Interval between doses (hrs)** Median (Range)	Duration of treatment (hrs)** Median (Range)
All patients	327	972	2.0 (1.0-10.0)	90 (28-450)	180 (28-6260)	3.0 (1.0-168.0)	8.0 (1.5-338.5)
N7	154	295	1.0 (1.0-10.0)	90 (48-272)	90 (48-1260)	3.0 (1.0-68.0)	4.0 (1.5-168.0)
N7OH	106	394	3.0 (1.0-10.0)	90 (28-300)	270 (28-6000)	3.0 (1.0-107.0)	12.5 (2.0-277.0)
N7P	13	39	2.0 (1.0-10.0)	90 (81-288)	243 (90-900)	3.0 (1.0-24.0)	4.0 (2.0-48.0)
N7POH	54	244	3.0 (1.0-10.0)	90 (36-450)	285 (40-6260)	3.0 (1.0-168.0)	26.0 (2.0-338.5)

Note: The doses of NovoSeven® for bleeding episodes were reported as single dose per infusion, date and time for the first 10 records. In cases with more than 10 records, only the total amount of the additional doses was collected. Two admissions have missing dose details and they are not included in this table.

*The number of additional doses is not recorded. Therefore maximum number of doses per admission is 10.

**Only calculated for admissions with more than one dose and with date and time of dose recorded.

Abbreviations: Adm = admission; hrs = hours; N7 = NovoSeven® alone; N7OH = NovoSeven® + other haemostatic treatment; N7P = NovoSeven® + platelets; N7POH = NovoSeven® + platelets + other haemostatic treatment

Table 13 rFVIIa dosing in bleeding episodes by bleed severity

Tx group	Total no. adm	Total no. doses*	No. doses per adm. Median (Range)	Dose per infusion (µg/kg) Median (Range)	Total dose per adm (µg/kg) Median (Range)	Interval between doses (hrs)** Median (Range)	Duration of treatment (hrs)** Median (Range)
Moderate bleedings							
All (N7)	262	614	2.0 (1.0-10.0)	90 (28-300)	92 (28-1260)	3.0 (1.0-70.0)	5.3 (1.5-168)
N7	154	295	1.0 (1.0-10.0)	90 (48-272)	90 (48-1260)	3.0 (1.0-68.0)	4 .0 (1.5-168)
N7OH	74	212	2.0 (1.0-10.0)	90 (28-300)	214 (28-1020)	3.0 (1.0-57.0)	10.0 (2.0-136.0)
N7P	13	39	2.0 (1.0-10.0)	90 (81-288)	243 (90-900)	3.0 (1.0-24.0)	4.0 (2.0-48.0)
N7POH	21	68	2.0 (1.0-10.0)	90 (50-186)	250 (83-900)	3.0 (1.0-70.0)	6.5 (3.0-81.0)
Severe bleedings							
All (N7)	65	358	5.0 (1.0-10.0)	90 (36-450)	450 (40-6260)	3.0 (1.0-168)	26 (2.0-338.5)
N7OH	32	182	5.0 (1.0-10.0)	90 (36-190)	450 (72-6000)	3.0 (2.0-107.0)	21.0 (2.0-277.0)
N7POH	33	176	5.0 (1.0-10.0)	90 (36-450)	450 (40-6260)	4.0 (1.0-168.0)	30.0 (2.0-338.5)

Note: Additional total dose in cases with more than 10 doses is only included in Total Dose per Admission. Two admissions have missing dose details and are not included in this table

*The number of additional doses is not recorded. Therefore maximum number of doses per admission is 10

**Only calculated for admissions with more than one dose and with date and time of dose recorded

Abbreviations: Tx = treatment; Adm = admission; N7 = rFVIIa alone; N7OH = rFVIIa+ other haemostatic treatment; N7P = rFVIIa + platelets; N7POH = rFVIIa + platelets + other haemostatic treatment

Dosing by refractoriness and antibody status

Regardless of refractory or antibody status, the median dose per infusion was generally similar (~ 90 µg/kg [range: 78−96 µg/kg]) and in line with the recommended and approved dose in GT (90 µg/kg) **Table 14**

Table 14 Dosing in bleeding episodes treated with NovoSeven – by refractoriness and antibody status

Refractoriness and antibody categories	Total no. adm	Total no. doses*	No. doses* per adm Median (Range)	Dose per infusion (µg/kg) Median (Range)	Total dose per adm (µg/kg) Median (Range)	Interval between doses (hrs)** Median (Range)	Duration of treatment (hrs)** Median (Range)
All patients	327	972	2.0 (1.0-10.0)	90 (28-450)	180 (28-6260)	3.0 (1.0-168.0)	8.0 (1.5-338.5)
Refr POS/AB POS	36	125	3.0 (1.0-10.0)	90 (40-450)	278 (40-4230)	3.0 (2.0-168.0)	9.0 (2.0-240.0)
Refr POS/AB NEG	31	177	5.0 (1.0-10.0)	90 (37-160)	574 (90-6260)	3.0 (1.0-114.0)	25.5 (2.0-338.5)
Refr POS/AB UNK	6	40	7.0 (3.0-10.0)	90 (90-90)	630 (270-1260)	3.0 (2.0-68.0)	27.0 (4.0-168.0)
Refr NEG/AB POS	43	172	3.0 (1.0-10.0)	96 (28-300)	270 (28-2760)	3.0 (2.0-25.0)	17.0 (2.0-72.0)
Refr NEG/AB NEG	157	257	1.0 (1.0-10.0)	90 (34-290)	90 (40-900)	3.0 (1.0-24.0)	4.0 (1.5-72.0)
Refr NEG/AB UNK	9	41	4.0 (2.0-9.0)	90 (26-111)	270 (72-810)	4.0 (2.0-57.0)	28.5 (3.0-136.0)
Refr UNK/AB POS	14	66	3.0 (1.0-10.0)	90 (62-360)	330 (90-1180)	4.0 (2.0-42.0)	52.0 (32.0-93.0)
Refr UNK/AB NEG	27	87	3.0 (1.0-10.0)	90 (70-170)	270 (80-1020)	3.0 (1.0-30.0)	4.8 (2.0-68.0)
Refr UNK/AB UNK	4	7	1.0 (1.0-4.0)	78 (78-128)	125 (96-312)	18.0 (3.0-19.0)	39.5 (39.5-39.5)

Note: Additional total dose in cases with more than 10 doses is only included in Total Dose per Admission. Two admissions have missing dose details and are not included in this table

*The number of additional doses is not recorded. Therefore maximum number of doses per admission is 10

Paediatric population

Dose

Regardless of age or treatment group, the median dose per infusion was similar, except for the N7P group, with only 1 admission in the adolescent group and a dose of 288 µg/kg.

Efficacy

In the N7 group, the treatment was effective in 84 (79%) bleeds in children, in 9 (82%) bleeds in adolescents and 35 (95%) bleeds in adults. In the N7OH group the proportion of effective treatments in children (84%) was higher than that of adults (76%) or adolescents (61%). In the N7POH group the proportion of effective treatments in children (69%) and adults (71%) were similar (Table 15).

Table 15 Efficacy in bleeding episodes by age

			Outcome (No. of admissions (%))				
Tx group	Age (years)	No. of adm	Effective	Partially effective	Ineffective	Not possible to evaluate	Not specified
All (N7)	<12	209	166 (79)	36 (17)	2 (1)	4 (2)	1 (0)
	12-17	35	22 (63)	12 (34)		1 (3)	
	≥18	87	72 (83)	12 (14)	2 (2)	1 (1)	
N7	<12	106	84 (79)	20 (19)		2 (2)	
	12-17	11	9 (82)	2 (18)			
	≥18	37	35 (95)	2 (5)			
N7OH	<12	62	52 (84)	6 (10)	2 (3)	2 (3)	
	12-17	18	11 (61)	6 (33)		1 (6)	
	≥18	29	22 (76)	5 (17)	1 (3)	1 (3)	
N7P	<12	9	8 (89)				1 (11)
	12-17	1	1 (100)				
	≥18	4	3 (75)	1 (25)			
N7POH	<12	32	22 (69)	10 (31)			
	12-17	5	1 (20)	4 (80)			
	≥18	17	12 (71)	4 (24)	1 (6)		

Abbreviations: Tx = treatment; Adm = admissions; N7 = rFVIIa alone; N7OH = rFVIIa + other haemostatic treatment; N7P = rFVIIa + platelets; N7POH= rFVIIa + platelets + other haemostatic treatment; OH = other haemostatic treatment; P = platelets; POH = other haemostatic treatment + platelets
Cross-reference: From EOT Table 14.2.8

Efficacy by treatment and by refractoriness and antibody status

In all patients, treatment with NovoSeven was evaluated as effective in 79% of the bleeding episodes (262 of 333 admissions). Further, in each treatment group, the majority of admissions were evaluated to be effective (range: 65%−86%). A summary of efficacy for bleeding episodes for the 4 treatment groups is shown in Table 16.

Irrespectively of refractoriness and antibody status, the majority of admissions were evaluated as effective (range: 56%−100%). When comparing the 3 categories 'without refractoriness and antibodies to platelets' (Refr NEG/AB NEG), 'with refractoriness but without antibodies to platelets' (Refr POS/AB NEG) and 'with refractoriness and antibodies to platelets' (Refr POS/AB POS), the effectiveness was similar in patients in these 3 categories (85%, 74% and 72%, respectively) and in line with effectiveness in all patients treated with NovoSeven (79%) Table 16.

Table 16 Efficacy in bleeding episodes by treatment and by refractoriness and antibody status

Treatment groups / categories	No. of adm	Outcome No. of admissions (%)				
		Effective	Partially effective	Ineffective	Not possible to evaluate	Not specified
All patients	333	262 (79)	60 (18)	4 (1)	6 (2)	1 (0)
Treatment groups						
N7	155	129 (83)	24 (15)		2 (1)	
N7OH	110	86 (78)	17 (15)	3 (3)	4 (4)	
N7P	14	12 (86)	1 (7)			1 (7)
N7POH	54	35 (65)	18 (33)	1 (2)		
Categories						
Refr POS/AB POS	36	26 (72)	10 (28)	-	-	-
Refr POS/AB NEG	31	23 (74)	6 (19)	1 (3)	1 (3)	-
Refr POS/AB UNK	6	6 (100)	-	-	-	-
Refr NEG/AB POS	47	30 (64)	12 (26)	2 (4)	3 (6)	-
Refr NEG/AB NEG	159	135 (85)	22 (14)	-	1 (1)	1 (1)
Refr NEG/AB UNK	9	5 (56)	4 (44)	-	-	-
Refr UNK/AB POS	14	11 (79)	2 (14)	1 (7)	-	-
Refr UNK/AB NEG	27	22 (81)	4 (15)	-	1 (4)	-
Refr UNK/AB UNK	4	4 (100)	-	-	-	-

Abbreviation: AB = antibody; adm = admission; N7 = NovoSeven® alone; N7OH = NovoSeven® + other haemostatic treatment; N7P = NovoSeven® + platelets; N7POH = NovoSeven® + platelets + other haemostatic treatment; NEG = negative; No = number; POS = positive; Refr = refractoriness; UNK = unknown

Paediatric population

In the age groups <12 years, 12–17 years and ≥18 years, the effectiveness in patients without refractoriness and antibodies to platelets (Refr NEG/AB NEG), was 83%, 82% and 95%, respectively. In patients with refractoriness but without antibodies to platelets (Refr POS/AB NEG), the effectiveness was 81%, 0% and 67%, respectively (in the age group 12–17 years, only 1 patient had 1 admission which was evaluated as 'partially effective'). In patients with refractoriness and antibodies to platelets (Refr POS/AB POS), the effectiveness were 68% and 76% (age groups <12 years and ≥18 years; there was no patients in the age group 12–17 years in this category) *(Table 6)*.

Dosing and efficacy - surgery

Dosing by treatment

As seen for bleeding episodes, there was a large variation in the dose per infusion of NovoSeven; however, the median dose in all patients (92 µg/kg; Table 4–8) was in line with the recommended and approved dose regimen in GT (90 µg [range 80–120 µg] per kg). The median dose was similar for all 4 treatment groups (90–95 µg/kg) (**Table 17**).

Table 17 Dosing in surgeries treated with NovoSeven – by treatment and severity

Tx group	Total no. adm	Total no. doses*	No. doses per adm. Median (Range)	Dose per infusion (µg/kg) Median (Range)	Total dose per adm (µg/kg) Median (Range)	Interval between doses (hrs)** Median (Range)	Duration of treatment (hrs)** Median (Range)
All (N7)	157	720	3.0 (1.0-24.0)	92 (4-270)	270 (4-8544)	3.0 (1.0-749.0)	5.0 (1.5-749.0)
N7	62	210	2.5 (1.0-21.0)	90 (70-250)	270 (80-6336)	2.0 (2.0-264)	4.0 (1.5-264.0)
N7OH	70	331	3.0 (1.0-22.0)	95 (25-270)	305 (90-8544)	3.0 (1.0-749.0)	5.5 (1.5-749.0)
N7P	4	45	8.5 (4.0-24.0)	90 (90-90)	765 (360-2167)	3.0 (1.0-12.0)	25.0 (8.0-126.0)
N7POH	21	134	3.0 (1.0-22.0)	90 (4-200)	270 (4-4617)	3.0 (1.0-18.0)	5.3 (2.0-139.0)
Major							
All (N7)	25	278	11.0 (1.0-24.0)	90 (25-240)	990 (180-6336)	3.0 (1.0-264.0)	48.5 (3.0-264)
N7	6	63	8.5 (2.0-21.0)	90 (90-240)	988 (180-6336)	3.0 (2.0-264.0)	48.0 (24.0-264)
N7OH	7	87	15.0 (2.0-22.0)	90 (25-120)	1800 (180-4424)	4.0 (1.0-30.0)	84.3 (3.0-198.5)
N7P	2	35	17.5 (11.0-24.0)	90 (90-90)	1579 (990-2167)	3.0 (1.0-12.0)	77.0 (28.0-126)
N7POH	10	93	6.0 (1.0-22.0)	90 (28-180)	397 (180-4334)	3.0 (1.0-18.0)	47.5 (3.0-139.0)
Minor							
All (N7)	132	442	2.5 (1.0-21.0)	100 (4-270)	270 (4-8544)	2.0 (1.0-749)	4.5 (1.5-749.0)
N7	56	147	2.0 (1.0-7.0)	95 (70-250)	251 (80-1250)	2.0 (2.0-26.0)	4.0 (1.5-68.0)
N7OH	63	244	3.0 (1.0-21.0)	100 (37-270)	300 (90-8544)	2.0 (1.0-749.0)	5.0 (1.5-749.0)
N7P	2	10	5.0 (4.0-6.0)	90 (90-90)	450 (360-540)	3.0 (2.0-6.0)	15.0 (8.0-22.0)
N7POH	11	41	2.0 (1.0-20.0)	133 (4-200)	180 (4-4617)	2.0 (2.0-6.0)	3.5 (2.0-54.0)

Note: Additional total dose in cases with more than 20 doses (prior to or during or after surgery) is only included in Total Dose per Admission. Two admissions have missing dose details and are not included in this table

*The number of additional doses is not recorded. Therefore maximum number of doses per admission is 3*20 (prior, during, after)

**Only calculated for surgeries with more than one dose, and with date and time of dose recorded. The dose interval at 749.0 is probably an outlier most likely due to an error in indication of timing of dosing.

Abbreviations: Tx = treatment; Adm = admission; N7 = rFVIIa alone; N7OH = rFVIIa+ other haemostatic treatment; N7POH = rFVIIa + platelets + other haemostatic treatment; N7P = rFVIIa + platelets

Cross-reference: From EOT Table 14.2.20 and 14.2.21

Paediatric population

The majority of surgical procedures treated with rFVIIa were performed in adults 134 (85%), with 17 (11%) in children and 6 (4%) in adolescents.

Dose

The median dose in the surgeries in the 6 adolescent patients was 120 µg/kg and was 90 µg/kg in the rest of the paediatric surgical admissions.

Efficacy

Efficacy in surgeries by age are shown in Table 18. Efficacy was lowest in children (50%) and adults (79%) treated in the N7POH group (**Table 18**).

Table 18 Efficacy – surgeries by age

Tx group	Age	No. of adm	Outcome (No. of admissions (%))			
			Effective	Partially effective	Ineffective	Not possible to evaluate
All (N7)	<12	17	13 (76)	3 (18)	1 (6)	
	12-17	6	6 (100)			
	≥18	136	121 (89)	11 (8)	2 (1)	2 (1)
N7	<12	3	3 (100)			
	12-17	4	4 (100)			
	≥18	55	52 (95)	3 (5)		
N7OH	<12	5	5 (100)			
	12-17	2	2 (100)			
	≥18	64	55 (86)	7 (11)	1 (2)	1 (2)
N7P	<12	1	1 (100)			
	≥18	3	3 (100)			
N7POH	<12	8	4 (50)	3 (38)	1 (13)	
	≥18	14	11 (79)	1 (7)	1 (7)	1 (7)

Abbreviations: Tx = treatment; Adm = admission; N7 = rFVIIa alone; N7OH = rFVIIa + other haemostatic treatment; N7POH = rFVIIa + platelets + other haemostatic treatment; N7P = rFVIIa + platelets
Cross-reference: From EOT Table 14.2.22

Dosing by refractoriness and antibody status

The median dose per infusion was generally similar across the refractoriness and antibody status categories (~90 µg/kg [range: 90−142 µg/kg]); however, for patients with refractoriness to platelets but without antibodies the median dose was slightly higher (142 µg/kg) Table 19 .

A large variation in total dose of NovoSeven and duration of treatment was seen; however, both total dose and duration of treatment was similar for patients without refractoriness and antibodies to platelets, patients with refractoriness but without antibodies to platelets and patients with refractoriness and antibodies to platelets (median total dose: 270 µg/kg, 315 µg/kg and 300 µg/kg, respectively; mean duration of treatment: 4.8 hours, 6.0 hours and 4.0 hours, respectively) Table 19.

Table 19 Dosing in surgery treated with NovoSeven – by refractoriness and antibody status

Refractoriness and antibody categories	Total no. adm	Total no. doses*	No. doses per adm Median (Range)	Dose per infusion (µg/kg) Median (Range)	Total dose per adm (µg/kg) Median (Range)	Interval between doses (hrs)** Median (Range)	Duration of treatment (hrs)** Median (Range)
All patients	157	720	3.0 (1.0-24.0)	92 (4-270)	270 (4-8544)	3.0 (1.0-749.0)	5.0 (1.5-749.0)
Refr POS/AB POS	40	120	3.0 (1.0-7.0)	102 (70-250)	300 (85-1250)	2.0 (2.0-26.0)	4.0 (1.5-68.0)
Refr POS/AB NEG	12	65	3.0 (1.0-20.0)	142 (85-200)	315 (90-4617)	2.0 (2.0-12.0)	6.0 (4.0-59.0)
Refr POS/ UNK	1	11	11.0 (11.0-11.0)	90 (90-90)	990 (990-990)	3.0 (1.0-6.0)	28.0 (28.0-28.0)
Refr NEG/AB POS	24	140	3.0 (1.0-22.0)	93 (4-270)	418 (4-5954)	3.0 (1.0-13.0)	7.0 (1.5-102.0)
Refr NEG/AB NEG	36	178	3.0 (1.0-22.0)	90 (28-180)	270 (80-6336)	3.0 (1.0-749.0)	4.8 (2.0-749.0)
Refr NEG/AB UNK	1	24	24.0 (24.0-24.0)	90 (90-90)	2167 (2167-2167)	4.5 (1.0-12.0)	126 (126.0-126.0)
Refr UNK/AB POS	20	84	3.0 (1.0-21.0)	95 (25-240)	354 (90-1988)	4.0 (2.0-264.0)	6.5 (2.5-264.0)
Refr UNK/AB NEG	23	98	2.0 (1.0-20.0)	90 (90-180)	180 (90-8544)	2.0 (1.0-30.0)	5.0 (2.5-97.5)

Note: The doses of NovoSeven® used prior, during and after a surgery were reported as single dose per infusion, date and time for the first twenty records. In cases with more than 20 records, only the total amount of the additional doses was collected.

*The number of additional doses is not recorded. Therefore maximum number of doses per admission is 3 times 20 (prior, during, after).

**Only calculated for admissions with more than one dose and with date and time of dose recorded

Abbreviations: AB = antibody; adm = admission; hrs = hours; N7 = NovoSeven® alone; N7OH = NovoSeven® + other haemostatic treatment; N7P = NovoSeven® + platelets; N7POH = NovoSeven® + platelets + other haemostatic treatment; NEG = negative; No = number; POS = positive; Refr = refractoriness; UNK = unknown

Efficacy by treatment and by refractory and antibodies

In all patients, a treatment including NovoSeven was evaluated as effective in 88% of the admissions (140 of 159 admissions). As seen for bleeding episodes, the majority of admissions in each treatment group were evaluated to be effective (range: 68%−100%). A summary of efficacy for all NovoSeven treatment groups is shown in Table 20.

Irrespectively of refractoriness and antibody status, the vast majority of admissions were evaluated as effective (range: 67%−100%). As seen for bleeding episodes, the effectiveness was similar in patients in the categories 'without refractoriness and antibodies to platelets', 'with refractoriness but without antibodies to platelets' and 'with refractoriness and antibodies to platelets' (95%, 67% and 95%, respectively) and in line with effectiveness in all patients treated with NovoSeven (88%). In the category 'with refractoriness but without antibodies to platelets', where 67% of the admissions was evaluated as effective (8 of 12 admissions), the remaining 33% (4 of 12 admissions) were evaluated as partially effective (Table 20)

Table 20 Efficacy in surgery by treatment and by refractoriness and antibody status

Treatment group / categories	No. of adm	Outcome No. of admissions (%)				
		Effective	Partially effective	Ineffective	Not possible to evaluate	Not specified
All patients	159	140 (88)	14 (9)	3 (2)	2 (1)	-
Treatment groups						
N7	62	59 (95)	3 (5)			-
N7OH	71	62 (87)	7 (10)	1 (1)	1 (1)	-
N7P	4	4 (100)				-
N7POH	22	15 (68)	4 (18)	2 (9)	1 (5)	-
Categories						
Refr POS/AB POS	40	38 (95)	2 (5)	-	-	-
Refr POS/AB NEG	12	8 (67)	4 (33)	-	-	-
Refr POS/AB UNK	1	1 (100)	-	-	-	-
Refr NEG/AB POS	25	21 (84)	2 (8)	1 (4)	1 (4)	-
Refr NEG/AB NEG	37	35 (95)	1 (3)	1 (3)	-	-
Refr NEG/AB UNK	1	1 (100)	-	-	-	-
Refr UNK/AB POS	20	14 (70)	4 (20)	1 (5)	1 (5)	-
Refr UNK/AB NEG	23	22 (96)	1 (4)	-	-	-

Abbreviation: AB = antibody; adm = admission; N7 = NovoSeven® alone; N7OH = NovoSeven® + other haemostatic treatment; N7P = NovoSeven® + platelets; N7POH = NovoSeven® + platelets + other haemostatic treatment; NEG = negative; No = number; POS = positive; Refr = refractoriness; UNK = unknown

Due to the low number of patients in the age groups <12 years and 12−17 years (0−5 patients) a comparison of these age groups in the 3 categories 'without refractoriness and antibodies to platelets', 'with refractoriness but without antibodies to platelets', and 'with refractoriness and antibodies to platelets ', is not considered relevant. In the age group ≥18 years, effectiveness in patients in the 3 categories was similar (100%, 73% and 94%, respectively) *(Table 9)*.

Published literature

A literature search was performed by Novo Nordisk Global Information and Analysis (GLIA) using BIOSIS Previews, Current Contents Search, Embase and MEDLINE. The literature review covered data from 01 January 1999 to 01 December 2017 and included only medical literature published in English. In all, 143 literature references were identified during the search, 14 of which contained sufficient predefined assessments of efficacy to warrant inclusion. All GT cases of treatment and prevention of bleedings (during delivery and surgery) in all ages and both genders in the reported period have been evaluated.

The MAH concludes that, overall, the published literature showed that a treatment regimen of NovoSeven alone, or based mainly on NovoSeven, reduces platelet transfusions, and seems to be effective and safe in patients with GT without antibodies to platelets, or where platelets are not readily available.

The MAH has provided detailed information on each of the 14 literature references in Appendix 2 of the Clinical Overview.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of Efficacy for trial Treatment of Glanzmann's Thrombasthenia: A

prospective observational registry

Title: Treatment of Glanzmann's Thrombasthenia: A prospective observational registry			
Study identifier	F7HAEM-3521 (GTR)		
Design	Observational		
	Duration of main phase:	7 years	
Hypothesis	to collect and evaluate the efficacy and safety of rFVIIa in patients with GT and past/present refractoriness to platelet transfusions.		
Treatments groups	Treatment with NovoSeven alone	62 patients	
	Treatment with NovoSeven in combination with antifibrinolytics	85 patients	
	Treatment with NovoSeven and/or platelets	11 patients	
	Treatment with NovoSeven combination with antifibrinolytics and/or platelets	45 patients	
Endpoints and definitions	Primary endpoint		To evaluate the efficacy and safety of rFVIIa during bleeding episodes and for the prevention of bleeding during invasive procedures/surgery in patients with GT with past or present refractoriness to platelet transfusions.
	Secondary endpoint		To describe the outcome of bleeding episodes and surgeries requiring systemic haemostatic treatment (with or without antifibrinolytic drugs or other agents) in patients with GT in real-life clinical settings
Database lock	16 December 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Observational			
Descriptive statistics and estimate variability	Treatment group	Novoseven, in patients refractory to platelet transfusions, in whom adequate haemostasis may not be possible.	Novoseven of admissions in patients not known to be refractory.	Novoseven surgical admissions, in patients refractory to platelet transfusions, in whom adequate haemostasis may not be possible
	Number of subject			
	endpoint	75%	79%	89%

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The **F7GLANZ** study (Glanzmann's thrombasthenia registry (GTR)) was designed as an observational, multinational registry to collect and evaluate the efficacy and safety of rFVIIa in patients with GT and past/present refractoriness to platelet transfusions.
The GTR was established in order to fulfil the commitment imposed by the EMA at the time of approval of the indication in GT requiring that efficacy and safety data were to be collected from patients with GT treated with rFVIIa. The focus was to be on dose regimens, efficacy and safety (especially the occurrence of thromboembolic complications in relation to concomitant use of anti-fibrinolytics).
Data were collected in 15 countries on the use of Novoseven as well as other treatments from January 2004 to December 2011 in GT bleeding episodes as well as prophylaxis for surgery. An external expert panel was responsible for giving scientific input regarding development, establishment and conduct of the GTR.

The GTR was a disease registry but was owned by Novo Nordisk A/S. Patients were treated in accordance with local treatment practices and no drugs were supplied.

Patient population
The only disease specific inclusion criterion was a diagnosis of GT, which could be made on the basis of platelet function / aggregation tests. As quantitative or qualitative evaluation of GPIIb/IIIa receptors including flow cytometry and identification of gene defects were optional diagnosis criteria, determination of the type of GT based on amount of GPIIb/IIIa i.e. Type I or Type II did not have to be performed. Thus it is not surprising that disease type was unknown in 114 (52%) patients.

There were no inclusion criteria specifying refractoriness to platelet transfusion or presence of anti-platelet antibodies. There were thus several possible combinations of refractoriness and presence of anti-platelet antibodies resulting in corresponding subgroups, some of which are very small.

Treatments
Any treatment considered justified by the physician could be used which is considered appropriate in this observational study. This may or may not have included Novoseven.

Sample size
With the data submitted in the 5th interim report, it was considered by the Rapporteur that sufficient data had been obtained to fulfil FUM 21.
The sample sizes of relevance to this Type II variation concern

- all patients in the GTR who were treated with Novoseven (n = 133) as they could potentially be patients *"for whom platelets are not readily available."*.
- the following subgroups of Novoseven treated patients:
  - all patients refractory to platelet transfusions as they include patients **with or without** antibodies to platelets (n = 31/133 (23%)) and
  - patients refractory to platelet transfusions but who are **without** antibodies to platelets (n=8/133 (6%)) as they were **not** covered by the currently approved indication of GT patients " *in patients with Glanzmann's thrombasthenia **with antibodies** to GP IIb - IIIa and/or HLA, **and** with past or present refractoriness to platelet transfusions."* This group is very small and efficacy has to be extrapolated from the other refractory patients and as well as from the other patients treated with Novoseven.

Efficacy outcomes

The main efficacy outcome was haemostasis based on a rating of clinical response (defined in Table 2 and Table 3) is reasonably in line, for example, with that mentioned in the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products *(EMA/CHMP/BPWP/144533/2009 rev. 1).* in which it is recommended that response should be assessed as "none", "moderate", "good" or "excellent" by the physician.

Considerations on data obtained from a registry
An advantage of this registry design is that data can be obtained over several years from a quite significant number of patients with a rare disease who are treated according to practice which is current at the treatment centres.

However, the observational nature of the study carries with it important limitations. For example, the reason for a patient to be given a particular therapy is according to physician's choice and open to bias.

There is also the possibility of underreporting of negative experiences as recognised by the MAH.

The GTR should give a picture of "real world" treatment of GT but this also introduces a confounding factor: although treatment with Novoseven was to be according to EU product information, physicians could use Novoseven in an open label manner according to their own medical judgement.

Within the GTR, meaningful comparisons between treatments are hardly possible as there are no pre-defined comparable subgroups. However, evaluation of the efficacy of Novoseven compared to other treatments was not the purpose of the registry.

Efficacy data and additional analyses

In the 6th Report, which included all patients up to closure of the registry in December 2011, the number of patients in the GTR had increased to 218 (1073 admissions) of whom 133 (492 admissions) were treated with Novoseven. 152 patients (581 admissions) had received treatment other than Novoseven. *(Patients may have been treated with or without Novoseven in different admissions meaning that the sum of patients who received Novoseven and those who did not is >218)).*
The 5th report had included 120 individuals (483 admissions) of whom 80 (197 admissions) were treated with Novoseven and 74 patients (286 admissions) received treatment other than Novoseven.

Thus at closure of the GTR, of 218 patients, more than half (133 (61%) received treatment with Novoseven either alone or in combination with platelet transfusion and/or other haemostatic therapy.
As the sequence of the haemostatic treatments used may be related to the efficacy of N7, in order to better understand the use of N7, the MAH was asked to provide the number of admissions for bleeding events where the first line treatment contained N7 (alone or combined) and to comment on a possible relation to efficacy of treatment with rFVIIa. From the information provided on efficacy rates according to treatment sequence (N7 as first line alone or in combination), it is not possible to conclude if it might be more beneficial to give N7 before administering other treatments.

Interestingly, as can be seen in Table 8, Novoseven was part of the treatment in 38% (333/870) of bleeding admissions compared to 78% (159/204) of surgical admissions. It is described in the 6th GTR report that the majority of procedures were elective (90%) and that rFVIIa was used prior, during and after surgery. In the majority of the rFVIIa-treated surgeries, rFVIIa was administered prior to surgery (141 of the 159 surgeries), and in many cases also after surgery (126 of 159 admissions). In 10 surgeries rFVIIa was used during the procedure. There was thus apparently a physician's choice to use Novoseven prior to elective surgery.

Notably, only 22/133 patients (16.5%) who received Novoseven in the GTR in any treatment combination were Refract POS / AB POS and received it in line with the currently approved GT indication.

<u>Number of patients treated with Novoseven for any admission (bleed or surgery):</u>

Of the 133 patients treated with Novoseven, 94 patients with 333 bleeding episode admissions and 77 patients with159 surgery admissions received Novoseven either alone (n=62 patients) or in combination with platelets and/or other haemostatic treatments.
Demographics and patient history have been presented. The MAH presented the baseline characteristics of patients and bleedings/surgeries separately for those treated with N7 and without N7. This included patient characteristics (age, sex, pregnancy, and disease type), location and severity of the bleeding episodes, type of surgery (minor/major).
These data showed that the main differences between the patients with bleeding episodes treated with N7 (n=94) and without N7 (n = 139) is that the first group is older (mean age 21.0 vs 15.7 years), presents more often with antibodies (41% vs 19%) and refractoriness (22% vs 9%). Similar differences are found in the surgical patients with N7 (n = 77) compared to those without N7 (n=36) with older age (mean 28.5 vs 24.6 years), antibodies (51% vs 36%), and refractoriness (29% vs 11%).

From information provided, it is evident that the characteristics of the bleeding episodes are not comparable, and therefore, no comparison between the efficacy of treatments with and without N7 can be performed.

Information on both refractory and antibody status was present for only 88 patients treated with Novoseven.

Numbers of refractory patients (n= 31) and haemostatic efficacy rating according to antibody categories and NovoSeven treatment were:

Refract POS / AB POS: 22 patients with 76 admissions (current indication).
Efficacy was rated as effective in 72% (26/36) of admissions for bleeds and 95% (38/40) for surgery.
14 patients in 31 admissions were treated only with Novoseven.

Refract POS / AB NEG: 8 patients with 43 admissions (covered by proposed modified (indication).
Efficacy was rated as effective in 74% (23/31) of admissions for bleeds and 67% (8/12 with rest partially effective) for surgery.
4 patients in 12 admissions were treated only with Novoseven.

Refract POS / AB unknown: 1 patient with 7 admissions.
Efficacy was rated as effective in all 6 admissions for bleeds and the single admission for surgery.
4 admissions were treated only with Novoseven.

Numbers of non-refractory patients (n = 63) and haemostatic efficacy rating according to antibody categories and NovoSeven treatment were:

Refract NEG / AB POS: 21 patients with 72 admissions (covered by proposed modified indication).
Efficacy was rated as effective in 64% (30/47) of admissions for bleeds and 84% (21/25)for surgery.
6 patients in 12 admissions were treated only with Novoseven.

Refract NEG / AB NEG: 37 patients with 196 admissions (covered by proposed modified indication).
Efficacy was rated as effective in 85% (135/159) of admissions for bleeds and 95% (35/37) for surgery.
18 patients in 125 admissions were treated only with Novoseven.

Refract NEG / AB unknown: 5 patients with 10 admissions.
Efficacy was rated as effective in 56% (5/9) of admissions for bleeds and the single admission for surgery.
One patient in one admission was treated only with Novoseven.

Keeping in mind the observational nature of the data and the fact that some subgroups are very small these haemostatic efficacy ratings can be considered to be similar over the various subgroups of refractoriness to platelet transfusions and antibody status.

Notably, similar efficacy ratings were reported in refractory patients (n=31 of whom 22 antibody positive patients were covered by the current indication) and in patients (n=63) not refractory to platelets who received Novoseven (off-label use) but who could potentially be treated on-label in the proposed modified indication as patients for whom platelets are not readily available.

In the admissions for bleeding events which were treated only with Novoseven (n=155) or with N7OH (n=110) – thus without platelets - the rate of effective treatment was approximately 80%. This is of relevance for the treatment of patients for whom platelets are not immediately available.

Severe bleeds / major surgery

Efficacy in bleeding events treated with Novoseven, was rated as effective in approximately 80% of the 265 admissions for bleeds of moderate severity (ineffective in 3 admissions) and approximately 60% to 70% of the 68 admissions for severe bleeds (ineffective in 1 admission).
This is in contrast with the small difference observed for bleedings treated without N7: 309/386 (80%) vs 119/151 (79%), respectively *(Summary Table 14.2.9 in CSR).* There was no explanation for this observation e.g. bleeding characteristics in the data could not provide an explanation for differences in bleeding efficacy in bleeding events treated with Novoseven compared to bleedings treated without N7. The registry data show that clinicians rarely administered N7 as first line treatment in severe bleedings in contrast with moderate bleedings. Although it cannot be concluded from the registry data that this is the sole explanation for the difference in outcomes as other bleeding characteristics were also different, in the view of the CHMP starting treatment with N7 as early as possible appears logical.

Efficacy in surgeries treated with Novoseven, was rated as effective in approximately 90% of the 133 admissions for minor surgeries (ineffective in 2 admissions) and in approximately 70% of the 19 admissions for major surgeries (ineffective in 1 admission).

Dosing
The median doses of Novoseven administered (~ 90 µg/kg) both in the treatment of bleeding episodes and in relation to surgical procedures, were as recommended in the approved posology for GT and the median intervals between doses (mostly 2 to 3 hours were close to that recommended for GT (every 1.5 to 2.5 hours). Doses used were similar regardless of refractory or antibody status but there was an apparent trend towards a higher median number of doses in patients refractory to platelet transfusions than in those not refractory.
The number of doses, total dose per admission and duration of treatment were higher in severe compared to moderate bleedings and in major surgery compared with minor surgery.

There was a wide range of doses used (28 to 450 µg/kg), wider than the SmPC recommendation (80-120 µg/kg). The MAH supplied histograms of the dose per infusion and the total dose per admission by type of surgery, by refractoriness/antibody status, and by age. The data of the registry indicate that clinicians in general follow SmPC recommendations.

Rationale for treatment of GT patients with Novoseven irrespective of refractoriness to platelet transfusion or anti-platelet antibody status

Although not completely understood, haemostatic efficacy of rFVIIa in GT is thought to be due to local enhancement of thrombin generation, mediated by rFVIIa, which increases adhesion of GPIIb/GPIIIa-deficient platelets which eventually facilitates fibrin formation and subsequent platelet aggregation. Mechanistically, there is not a reason to expect that rFVIIa would work differently in patients who are refractory to platelet transfusions either because of clinical factors at the time of bleeding or because of antiplatelet antibodies.

The desirability of being restrictive with platelet transfusions in subjects with a severe GT phenotype, for whom immunisation to platelets may present a serious and possibly life threatening risk of lack of efficacy

of platelet transfusions at a time of major bleeds, is also a factor for consideration in relation to the possibility of alternative treatment with rFVIIa.
The need to prevent immunisation in women of childbearing age, which might cause immune mediated foetal or neonatal thrombocytopenia, is another reason for restricting use of (unmatched) platelets if possible.

Assessment of paediatric data on clinical efficacy

Overall in the paediatric age range, dosing and haemostatic efficacy in the treatment of bleeds and surgical procedures were similar to that reported in patients ≥18 years.

2.4.3. Conclusions on the clinical efficacy

In admissions for both the treatment of bleeding events and in the prevention of bleeding in patients undergoing surgical interventions the following can be concluded:

- Median dose range and dosing interval for Novoseven were within the currently recommended posology
- High rates of haemostatic efficacy and very few reports of treatment being ineffective with Novoseven were seen in the majority of admissions with treatment in 64% up to 80% rated as effective for bleeding admissions and 67% up to 95% rated as effective in surgical admissions.
- There was no apparent difference in the ratings of haemostatic efficacy in the different subgroups according to treatment combinations (with platelets and/or other haemostatic therapy) or according to refractoriness to platelet transfusions or antibody status.

The efficacy of eptacog alfa for this updated indication is considered sufficiently demonstrated.

2.5. Clinical safety

Introduction

The evaluation of safety in this variation application is based on:

- The GTR,
- Single-cases with adverse drug reactions published in the literature, and
- Novo Nordisk safety surveillance database (ARGUS) with spontaneous reports, solicited reports from post-authorisation studies and registries, and reports published in the literature.

The safety analysis population from the GTR includes all patients treated with NovoSeven in the registry.

Given that no adverse events have been reported in patients with GT exposed to NovoSeven during clinical trials, and all adverse events reported are obtained from post-marketing spontaneous report and the published literature, the frequency of adverse drug reactions cannot be assessed.

Patient exposure

Glanzmann's thrombasthenia registry

In all, 133 patients with 492 admissions were treated with NovoSeven; 94 patients with 333 admissions for bleeding episodes and 77 patients with 159 admissions for surgical procedures.

A summary of overall exposure per patient, including number of admissions, number of infusions, median

dose/infusion, median total dose per admission as provided by the MAH in response to the RfSI is given below (Table 21).

Table 21 Summary of rFVIIa Dosing for Bleeding Episodes and Surgeries Treated with rFVIIa

Treatment group	No. of Subjects	No. of Admissions	No. of Doses #	No. of Doses per Adm.			Dose per Inf. [µg/kg]			Total Dose per Adm. [µg/kg]		
				Median	Min	Max	Median	Min	Max	Median	Min	Max
All	132	484	1692	2.0	1.0	24.0	90	4	450	202	4	8544
N7	62	216	505	1.0	1.0	21.0	90	48	272	116	48	6336
N7OH	84	176	725	3.0	1.0	22.0	90	25	300	270	28	8544
N7P	11	17	84	3.0	1.0	24.0	90	81	288	270	90	2167
N7POH	44	75	378	3.0	1.0	22.0	90	4	450	270	4	6260

Adverse events

In the GTR, 15 adverse events were reported in 9 patients. Of these 15 adverse events, 8 were non-serious and 7 were serious (Table 22). Narratives on these 9 patients are provided in **Table 23**. No deaths were reported in patients receiving NovoSeven.

Table 22 Summary of admissions and adverse events in the GTR (all treatments)

	Treatment including rFVIIa			Treatment not including rFVIIa			Total*		
	No. Patients	No. Adm#	No. Adverse Events	No. Patients	No. Adm#	No. Adverse Events	No. Patients	No. Adm #	No. Adverse Events
No. of Admissions	133	492		152	581		218	1073	
Adverse Events, n	9	11	15	10	16	31	18	31	46
Serious, n	4	5	7	1	1	8	5	10	15
Non-serious, n	6	6	8	10	15	23	15	21	31

*The total number of patients and admissions include the 4 admissions that only have adverse event information (and thus no treatment). # Number of admissions.

Two patients treated with NovoSeven had adverse events that were assessed by the investigator as 'possibly/probably' related to NovoSeven; 'Nausea', 'Dyspnoea' and 'Headache' in 1 patient (non-serious) and 'Deep vein thrombosis' in 1 patient (serious).

The type and severity of adverse events do not indicate a difference between patients with or without refractoriness and patients with or without antibodies to platelets. However, the number of adverse events reported in the GTR is rather low and is a limiting factor for comparing the categories.

Table 23 Adverse events in the GTR (treatments including NovoSeven)

Patient (Adm)	Adverse events	Refractoriness and antibody status Description
2012 (379)	Allergic reaction: Shaking chills (non-serious)	Refractoriness: Negative. Antibodies: Negative. The patient (57 years at admission, type II GT) had a minor surgery (excision) 21 April 2009. Prior to surgery, the patient received NovoSeven (104 µg/kg), 10 units of single donor platelets and tranexamic acid. After the surgery, the patient received NovoSeven (69.5 µg/kg) and tranexamic acid. The patient's haemoglobin concentration was similar before (13.9 g/dL) and after (14.1 g/dL) surgery. The patient had an allergic reaction specified as non-serious shaking chills 21 April 2009. The adverse event was judged to be unlikely related to NovoSeven. The patient stayed 2 days in the hospital and recovered completely.
2016 (259)	Bacterial infection (non-serious)	Refractoriness: Positive. Antibodies: Negative. The patient (11 years at admission, type I GT, refractory to platelet transfusion) had a spontaneous severe gum bleeding 28 October 2008. Prior to NovoSeven, he was treated with anti-fibrinolytics, estrogens, red blood cell (RBC), fresh frozen plasma and local tamponade. He received the first dose of NovoSeven 29 October 2008 at 12:00 hours. The treatment with NovoSeven (at doses of 80 µg/kg or 160 µg/kg) continued until 10 November 2008. The patient received other antifibrinolytic agents from 28 October 2008 to 3 November 2008, tranexamic acid from 29 October 2008 until 10 November 2008 and other product from 2 November 2008 to 4 November 2008. The patient had a bacterial infection via local tamponade 6 hours after the first dose of NovoSeven. The adverse event was judged to be unlikely related to NovoSeven and the patient recovered completely.
2016 (370)	Septicaemia, respiratory insufficiency and cardiac decompensation (serious)	Refractoriness: Positive. Antibodies: Negative. The patient (11 years at admission) had serious epistaxis and pharyngeal bleeding 19 February 2009 at 04:00 hours. The biopsy showed ulcerative mucosa. He received an endotracheal intubation, a Blalocq tamponade. In addition, he received NovoSeven (over 60 doses in total from 19 to 24 February 2009), standard platelets (from 22 to 24 February 2009), RBC transfusions, tranexamic acid (from 19 to 24 February 2009) and other antifibrinolytic agents (from 19 to 24 February 2009) to stabilise his condition. The patient developed septicaemia, respiratory insufficiency and cardiac decompensation 6 hours after the first dose of NovoSeven. The adverse event was serious and judged to be unlikely related to NovoSeven. The patient recovered completely.
2016 (483)	Sub – arachnoideal bleeding	Refractoriness: Positive. Antibodies: Negative. The patient (11 years at admission) had a subarachnoideal bleeding found on a CT scan 02 March 2009. There was minimal blood on the brain

	(serious)	surface on the CT scan. The adverse event was serious and judged to be unlikely related to NovoSeven and the patient recovered with sequelae.
2057 (489)	Re-bleeding and hematoma due to a fall (serious)	Refractoriness: Negative. Antibodies: Positive. The patient (1 year at admission, type I GT) had epistaxis and ubcutaneous haematoma (traumatic) 10 December 2004 at 12:00. The patient was treated with 7 doses of 85 µg/kg NovoSeven, The dosing started 1 hour after bleeding start (i.e., 13:00 hours). The treatment was effective. The adverse event was serious and judged to be unlikely related to NovoSeven. The patient recovered completely.
2066 (1580)	Fever (non-serious)	Refractoriness: Negative. Antibodies: Missing. The patient (12 years at admission) had asthenia and gum bleeding several days before admission. The morning before admission the patient had haematemesis (vomiting of blood). The patient was treated with 2 doses of 36 µg/kg NovoSeven separated by 3 hours and RBC. The treatment was effective. The patient had a fever 6 hours after the first dose of NovoSeven. The adverse event was judged unlikely related to NovoSeven treatment.
2092 (696)	Pyrexia of 38.5 degrees Celsius (non-serious)	Refractoriness: Negative. Antibodies: Negative. The patient (1 year at admission, type I GT) underwent a circumcision on 29 May 2009 at 09:30. The patient received 1 unit RBC 12 hours prior to surgery. The patient was treated with 0.5 units of HLA-compatible platelets 30 minutes prior to and during surgery. The patient was also treated with tranexamic acid prior to and after surgery. The patient received 180 µg/kg NovoSeven 7 hours after the surgery began. The adverse event was non-serious and judged to be unlikely related to NovoSeven. The patient recovered completely..
2119 (650)	Headache (non-serious)	Refractoriness: Negative. Antibodies: Positive. The patient (9 years at admission, unknown GT) had bleeding from a tooth falling out on 9 March 2010 at 19:00. The patient was treated with NovoSeven (2 doses of 186 and 185 µg/kg, 8 hours apart), 500 mg tranexamic acid, and 1 unit of platelets. The treatment was evaluated as effective. The adverse event was non-serious and judged to be unlikely related to NovoSeven. The patient recovered completely.
2197 (1380)	Thrombotic events; deep vein thrombosis (serious)	Refractoriness: Positive. Antibodies: Negative. The patient (25 years at admission, type I GT) underwent an emergency laparotomy (ovarian cyst and haematoma with bilateral ureteral compression) on 06 June 2011 at 22:00. The patient was treated with 19 doses of 142 µg/kg NovoSeven at 2−3 hour intervals starting at 22:00 and treatment was partially effective. The patient was also treated with 5 units of RBC within 24 hours after surgery and 3 units of platelets. The patient developed deep vein thrombosis. The adverse event was serious and judged to be probably or possibly related to NovoSeven. The patient did not recover.

		Company comment: In this patient, the use of platelets transfusions and the surgical procedure (usually associated with immobilisation) are confounding aetiology factors for the venous thromboembolic event.
2213 (1056)	Nausea, dyspnea and headache (non-serious)	Refractoriness: Negative. Antibodies: Positive. The patient (25 years at admission, type I GT and antibodies against GPIIb-IIIa) had flare-up of menorrhaghia 5 days after first dose of triptoreline. There was a drop of haemoglobin level from 8 g/dL to 6.4 g/dL within 24 hours 4 days after the last dose of NovoSeven (96 hours). The patient received NovoSeven (total dose 1840 µg/kg), RBC and tranexamic acid. After doses of NovoSeven injected on 21 March 2010 the patient had nausea, dyspnea and headache. A pulmonary embolism or a cerebral thromboembolic event were ruled out by a cerebral tomodensitometry and a pulmonary angioscanner. Both were normal. NovoSeven was interrupted 24 March 2010 at 20:00 hours because judged not enough effective to stop bleeding episode moreover concomitant nausea and dyspnea were noticed after injections. The investigator judged the events as probably or possibly related to NovoSeven, however commented: 'effects of concomitant hormonal treatment, anemia and transfusions of RBC may have also played a role'. Washed RBCs were given to avoid anti-platelet immunisation. Bleeding was significantly decreased after NovoSeven reintroduction on 25 March 2010 14:00 hours, indicating a significant effect (even partial) and therefore was continued until 30 March 2010. However, complete cessation of bleeding might be related to the effect of the hormonal therapy and the end of the flare-up phenomenon (typical duration of 6 days). The adverse events were serious and judged to be probably or possibly related to NovoSeven.
2290 (1094)	Rectorragia (serious)	Refractoriness: Unknown. Antibodies: Positive. The patient (45 years at admission, type I GTa) underwent a colonoscopy with polypectomy on 06 July 2005. The patient was treated with 87 µg/kg NovoSeven prior to the procedure and 13 doses (87 µg/kg) NovoSeven and tranexamic acid after the procedure. The treatment was evaluated as partially effective. The adverse event was serious and judged to be unlikely related to NovoSeven. The patient recovered completely.

Post marketing experience

Post-marketing safety data including cases published in the literature

Safety data from the marketed use of NovoSeven has been collected in the Novo Nordisk safety database ARGUS since the first marketing authorisation on 28 December 1995, and specifically for GT since the first approval in EU in 2004.

Up to 01 December 2017, 53 cases (34 from spontaneous sources, 2 solicited and 17 from the scientific literature), comprising 77 adverse drug reactions (43 serious and 34 non-serious; 47 spontaneous, 2

solicited and 28 from the scientific literature) have been reported cumulatively from post-marketing sources within the indication of GT.

Six case reports had a fatal outcome (1 reported in the literature and 5 reported spontaneously). Of these, 3 cases concerned patients with severe haemorrhage, and 2 concerned thromboembolic adverse drug reactions; no information is available on the sixth case. The analysis of the fatal cases did not raise any safety concerns. The fatal cases are described separately below.

Important identified risks

Based on the cumulative experience with NovoSeven, the important identified risks relevant for NovoSeven in GT and the number of adverse drug reactions reported post-marketing are presented in Table 24 and discussed below. Immunogenicity is only an identified risk for congenital factor VII deficiency and is therefore not described for GT.

Table 24 Important identified risks and number of adverse drug reactions in Glanzmann's thrombasthenia (post-marketing, including serious adverse drug reactions from the GTR)

Adverse drug reaction	Number of serious adverse drug reactions	Number of non-serious adverse drug reactions	Total
Arterial thromboembolic events	1	-	1
Venous thromboembolic events	9	-	9
Mixed thromboembolic events	4	1	5
Lack of efficacy	7	17	24
Allergic reactions[a]	3	-	3
Total	24	18	42

[a]MedDRA narrow scope terms only

Arterial thromboembolic events

One case comprising a serious adverse drug reaction was reported as 'Ischaemic stroke'. It concerned a 54-year old female who was treated simultaneously with NovoSeven and platelets. After 72 hours of this concomitant therapy, the patient developed mental confusion. An MRI showed an ischaemic lesion of the left insular area with left M2 occlusion. The patient recovered from the event. No information about refractoriness or platelet antibodies was reported for this patient.

Venous thromboembolic events

A total of 8 cases comprising 9 serious adverse drug reactions concerning venous thromboembolic events have been reported cumulatively. Of these, 3 serious cases were reported as 'Pulmonary embolism' (1 with a fatal outcome, described below and also co-reported with 2 mixed thromboembolic events) and 4 as 'Deep vein thrombosis' (1 case was reported as both 'Deep vein thrombosis' and 'Pulmonary embolism'). One case of 'deep vein thrombosis' was reported from the GTR. The other 2 serious cases were reported as 'Jugular vein thrombosis' and 'Retinal vein thrombosis'. The analysis of these cases did not raise any safety concerns.

Mixed thromboembolic events

Three cases (2 serious and 1 non-serious) concerned mixed (arterial and venous) thromboembolic events. The non-serious case was reported as 'Cerebrovascular accident' in a 30-year old female patient who recovered with sequelae. The 2 serious cases were reported as 'Disseminated intravascular coagulation' and 'Thrombosis' (with a fatal outcome) and as 'Atrial thrombosis' and 'Intracardial

thrombus' (also with a fatal outcome and with co-reported as 'Pulmonary embolism'). The fatal cases are described below. The analysis of these cases did not raise any safety concerns.

Lack of efficacy

A total of 21 cases concerned lack of efficacy. Of these, 7 were serious cases and all were reported in female patients. Six of the serious cases were reported in the literature and concerned patients who underwent major surgical procedures (4 cases) and 2 concerned patients with unsuccessful treatment of epistaxis. The last case was spontaneous and concerned a patient who underwent a dental extraction. There were 14 non-serious cases reported, 5 from the literature and 9 from spontaneous sources. Of the 14 non-serious cases, 13 were reported as 'Drug ineffective' and 1 as 'Therapeutic response decreased'. The analysis of these cases did not raise any safety concerns. Of the 21 cases concerning lack of efficacy, information about positive refractoriness or antibodies against platelets was reported for only 4 of the cases. The rest of the cases (17) did not have this information available or reported.

Allergic reactions

Two spontaneous serious cases concerned allergic reactions. The first case concerned an 8-year old male patient who underwent a surgical procedure and developed angioedema 2 hours after NovoSeven administration. The patient also received tranexamic acid and thrombocytes concentrate, which are confounding aetiology factors. The other case concerned a 39-year old female patient who experienced an anaphylactic reaction with angioedema and urticaria during treatment with NovoSeven. The analysis of these cases did not raise any safety concerns.

Fatal cases

In total, 6 cases with a fatal outcome have been reported cumulatively; 1 reported in the literatureand 5 reported spontaneously. For none of the cases, information on refractoriness or platelet antibodies was available. The analysis of the 6 cases with a fatal outcome did not raise any safety concerns. A brief narrative of each case is provided below and detailed narratives on the fatal cases are provided in Appendix 3 of the Clinical Overview.

Literature case

The case (case 321755; 'Atrial thrombosis')38 concerned a 30-year old female who experienced uncontrollable epistaxis, unsuccessfully treated with several red blood cells and platelet transfusions. After undergoing transcatheter embolisation of various cephaleal arteries, she developed severe haematuria, melena, conjuntival, oropharyngeal, vaginal and diffuse alveolar haemorrhages for which she was treated with 3 doses of NovoSeven. The following day she was found in asystole and attempts to resuscitate her failed. Autopsy results revealed thrombi in the right atrium and ventricle and within the pulmonary vessels.

Spontaneous cases

One case (case 234505; 'Intestinal ischaemia') concerned a 15-year old male who underwent surgery due to perforated appendicitis. Three days after the appendicectomy the patient underwent a laparatomy which revealed bowel necrosis, and subsequently another laparatomy performed 6 days after the appendicectomy revealed that his entire stomach and bowels were necrotic. The patient was treated with NovoSeven in various occasions before, during, and after the appendicectomy.

One case (case 261368; 'Disseminated intravascular coagulation', 'Thrombocytopaenia, 'Postoperative renal failure', 'Thrombosis', and 'Cerebral haemorrhage') concerned a 46-year old female who underwent vaginal hysterectomy. Despite prophylaxis with NovoSeven, the patient had diffuse bleeding during the surgery and postoperatively and was treated with various infusions of platelets. The patient then developed disseminated intravascular coagulation, thrombocytopenia and renal failure, and posteriorly

generalised microthrombosis, for which she was treated with heparin, leading to intracranial haemorrhage. She underwent a craniotomy for removal of the haematoma and died 1 month later.

One case (case 413570; 'Haemorrhage') concerned a 7-year old female patient who was admitted to the hospital due to severe haemorrhage (type not reported). The patient was treated with NovoSeven (dates and doses unknown). It was reported that the patient died due to serious bleeding complications. No further information is available.

One case (case 425990; 'Death') was reported by a nurse for a patient (age and gender unknown) who was treated with NovoSeven and died (dates of treatment, doses and date of death unknown). No further information is available for this case.

One case (case 477168; 'Vaginal haemorrhage') concerned a 13-year old female who was admitted to the hospital due to vaginal haemorrhage. The patient was treated with NovoSeven and developed complications (not specified) and died. No further information is available about this case.

Refractoriness and antibodies against platelets

Of the 53 cases reported in the Novo Nordisk safety database ARGUS up to 01 December 2017, information on refractoriness and/or antibodies to platelet is available on 11 cases; an overview of these cases is provided in Table 25 and details are given in narrative line listings in Appendix 3 of the Clinical Overview. For the remaining 42 cases, no information on refractoriness and antibody status is available.

Due to the low number of cases with information on refractoriness and/or antibodies to platelet (11 of the 53 cases), a comparison between the categories with and without refractoriness and/or antibodies to platelet is not possible. However, the type and severity of adverse events in patients with refractoriness and/or antibodies to platelet does not indicate that the safety profile of NovoSeven differs from patients where no information on refractoriness and/or antibodies to platelet is available.

Table 25 Cases with information on refractoriness and/or platelet antibodies

Case number	Report type	Patient (Age/sex)	Preferred term	Refractoriness/platelet antibodies
360434	Literature[29]	35/Female	Drug ineffective	Refractoriness
329740	Spontaneous	8/Male	Hepatic enzyme increased	Refractoriness
320758	Literature[35]	48/Female	Epistaxis/Jugular vein thrombosis	Refractoriness/Antibodies +
516136	Spontaneous	70/Female	Pulmonary embolism	Antibodies +
204311	Literature[33]	72/Female	Pulmonary embolism/Drug ineffective/Deep vein thrombosis	Iso-antibodies +
460757	Spontaneous	37/Male	Deep vein thrombosis	Reported as 'Low-symptomatic but with history of severe anti-HLA thrombocytic alloimmunization and history of anti-GPIIb-IIIa isoimmunization'
235689	Spontaneous	-/Female	Phlebitis	Antiplatelets antibodies
447932	Spontaneous	54/Female	Drug ineffective	Reported as 'Immunised'
520640	Literature[36]	38/Female	Pregnancy	Anti-Human Platelet Antigen +
377230	Literature[30]	6/-	Drug ineffective	The title of the publication states 'anti-platelet antibodies' but not in the narrative
332359	Solicited	25/Female	Deep vein thrombosis	Refractoriness

Cross-reference: Narrative line listings in Appendix 3

2.5.1. Discussion on clinical safety

Adverse events reported in the GTR

In the GTR there was a low number of AEs reported in patients who had received Novoseven with 15 AEs in 9 patients in 11 admissions (133 patients had been treated with Novoseven in 492 admissions). There was one report of deep vein thrombosis (judged to be probably or possibly related to rFVIIa treatment), 3 reports of bleeding (judged to be unlikely related to rFVIIa treatment), 2 reports of infection and 2 reports of headache and a report of nausea and dyspnoea (pulmonary embolism ruled out by imaging investigation).

For comparison, 152 individuals had received treatment which did not include Novoseven in 581 admissions. There were 31 adverse events in 11 patients reported in 20 admissions in which the treatment included other haemostatic treatment than rFVIIa or treatment was not registered.
These AEs consisted mainly of allergic reactions and fever/ chills (14 cases), almost all of which occurred in patients who had received erythrocyte or platelet transfusions and 5 reports of infections. There were no reports of thromboembolic AEs.

Thus in the GTR, adverse events were reported in 9/133 (~7%) of Novoseven treated patients in 11/492 (~2%) admissions. AEs were reported in 11/152 (also ~7%) of patients treated without Novoseven in 20/581 (~3.5%) admissions. These rates of AE reporting are very similar.
Overall, the type of AEs reported from the GTR can be considered as being consistent with the known safety profile of the treatments being given and of the bleeding diathesis seen with GT.

Adverse events <u>from post-marketing data</u>

Of the 24 serious adverse drug reactions (ADRs), 14 were thromboembolic events, 7 were lack of efficacy and 3 were allergic reactions. Of the 18 non-serious ADRs, one was a thrombotic event and 17 were lack of efficacy.

Looking at the narratives in the Clinical overview, there were some reports dating from 1999, early 2000's and a considerable number in the last decade including up to 2017. These reports illustrate the complications and adverse events which can arise in the treatment of (serious) bleeds, especially mucocutaneous bleeds such as epistaxis, vaginal bleeding and gastrointestinal bleeding in patients with GT.

Some reports show the events occurring in patients when bleeding is difficult to treat, requiring additional haemostatic treatment but also increasing the risk of thrombotic events while at the same time the bleed is not adequately controlled.

The most striking reports are those of the 6 fatal cases (for 3 of which there is little information available) dated between 2003 and 2016, one from the literature and five from spontaneous reporting.
For example Case 261368 concerned a 46 year old woman undergoing vaginal hysterectomy who received concentrated platelets, tranexamic acid and Novoseven pre-operatively. For continued diffuse bleeding during the operation and also post-operatively she received Novoseven, concentrated platelets and erythrocyte transfusions. Post-operatively she developed disseminated intravascular coagulation, thrombocytopenia and renal failure and received heparin. Intracerebral bleeding occurred, for which she received Novoseven, FXIII and other coagulation factors. This patient died about 5 weeks after the hysterectomy.

It is noted that in 4 of the serious post-marketing cases Novoseven was administered by continuous infusion. In all of these there was lack of efficacy reported (this is mentioned in association with continuous infusion in the treatment of GT in the Novoseven SmPC) and in 2 of these there was also a venous thrombosis (one case of DVT and one of pulmonary embolus).

The fatal cases 3 of which were in patients aged 15 years, 7 years and 13 years, also show that treatment of haemorrhage due to GT, in some cases possibly with complications arising from treatment or with poor response to treatment may still result in death even in paediatric patients.

Adverse events in relation to refractoriness to platelet transfusions or antibody status

GTR

With regard to safety in the proposed modified indication as reported in the GTR, there were 9 Novoseven treated patients who experienced 15 AEs.
Numbers of patients and refractory and antibody status are shown below.

Ref Pos / AB Neg	Ref Neg / AB Neg	Ref Neg / AB Pos	Ref Neg / AB missing	Ref Unknown/ AB pos
2	2	3	1	1

Post-marketing data

For the 53 post-marketing and literature reported cases, there was information on refractoriness and antibody status in only 11 cases.
For these, 3 cases were refractory only, 6 with antibodies (and one "immunised") but not refractory and in one case the patient was refractory and had antibodies.

The small number of adverse events reported in Novoseven treated patients in the GTR and the few patients in the literature reports with information on refractory/antibody status, mean that definite conclusions on safety for subgroups according to refractoriness or antibody status cannot be drawn. On the other hand there are no suggestions that the safety profile of Novoseven should differ in these subgroups.

However, it is of importance that patients can be treated at least with HLA matched platelets in order to prevent refractoriness to platelet transfusion.

For both the GTR reports and the post-marketing reports, the adverse events and safety profile according to concomitant haemostatic treatment have not been presented. It is not immediately obvious that this information may be relevant to the proposed modification of the indication. However, there may be an increased risk of thrombosis including disseminated intravascular coagulation in patients not responding to treatment with platelet transfusions and requiring intensive haemostatic treatment to control continuing bleeding (e.g. Case 261368 in which the patient died).

One of the objectives of the GTR was to focus on the administered dose regimens, and safety (especially the occurrence of thromboembolic complications in relation to concomitant use of anti-fibrinolytics). As additional post-marketing safety data is available since the 5th interim report from the GTR and as almost half the patients treated with Novoseven in the GTR were <18 years old, the MAH was asked to present and to discuss adverse events, both from post-marketing sources and from the GTR:

- in relation to treatment with Novoseven concomitantly with platelet transfusions and other haemostatic therapies such as antifibrinolytic agents,
- in relation to the Novoseven dosing regimen (including continuous infusion),
- in relation to whether the patient was refractory to platelet transfusions or had antibodies to GPIIb/IIIa or HLA and
- according to the age groups <12 years, 12 to <18 years and ≥18 years.
- The MAH is asked to consider if additions or changes to the safety information in the Novoseven SmPC would be appropriate based on this analysis.

The MAH provided a detailed overview of these points which leads to the following conclusions:
The post-marketing data on the occurrence of TEE in patients treated with Novoseven showed that in a high proportion of these cases there was concomitant therapy with antifibrinolytic agents. However, there was also a confounding factor involved in 7 of these 8 cases.
Furthermore, in post-marketing data only cases of adverse events are reported, it is not known how large the population of GT patients is in which antifibrinolytic agents are used concomitant to Novoseven. There are thus no comparative data in which to assess the frequency of TEE in GT patients treated with Novoseven with or without concomitant antifibrinolytic agents or other additional haemostatic therapy.
While it seems plausible that combined use of Novoseven with antifibrinolytic agents in patients with GT would increase the risk of TEE, no firm conclusion can be drawn from the available data.

From the information provided, almost of the reported doses were close to or within the recommended dosing range for GT and overall no concerns arise from the reported doses.

With the small number of subjects and AEs reported in the GTR (15 AEs reported in 9 subjects), it is not possible to make any relation between AEs and age or between AEs and status with respect to antibodies or refractoriness to platelet transfusions. In any case there was no predominance of an age group in the reporting of AEs in the GTR.
In the post-marketing reports, the majority of patients (18 of 29) were aged >18 years, 2 were aged 2 – 17 years and 6 aged <12 years. There is thus only limited information on patients aged <18 years and no information about the age distribution in the patient population from which these reports originate.

No relationship was evident between refractoriness to platelet transfusions or presence of antibodies to GPIIb/IIIa or HLA.

Based on the further analysis of the safety data obtained in the GTR and post-marketing, there is no need for additions or changes to the current safety information in the SmPC for Glanzmann's Thrombasthenia patients.

Assessment of paediatric data on clinical safety

Based on available data, the safety profile in the paediatric population does not appear to be different to that in adults. Paediatric patients with GT are also at risk of thromboembolic complications in relation to treatment with Novoseven.

2.5.2. Conclusions on clinical safety

Definite conclusions on safety for subgroups according to refractoriness or antibody status cannot be drawn. However, there are no suggestions that the safety profile of Novoseven should differ in these subgroups and no safety issues have been identified which would preclude broadening of the indication in GT to:

"Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions or where platelets are not readily available."

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Venous thromboembolic events Arterial thromboembolic events Immunogenicity (FVII deficiency)
Important potential risks	Immunogenicity (potential risk for acquired haemophilia, congenital haemophilia A and B, Glanzmann's thromboasthenia)
Missing information	Elderly patients Pregnant and lactating women Single high-dose use (270 µg/kg; in haemophilia A and B with inhibitors)

Some of the existing important identified risks (lack of efficacy, allergic reaction) and important potential risks (use outside approved indications) were removed from the list of safety concerns as a result of the transition to the new RMP template revision 2 in accordance with the new GVP module V. The MAH should continue to provide an update of allergic reactions in the PSURs. The MAH should continue to monitor use outside of approved indications in the PSURs, including a separate description of adverse events reported with use outside of the approved indication.

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place:

- Immunogenicity questionnaire
- Embolic and thrombotic events questionnaire
- Antibody testing is offered.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Venous thromboembolic events	*Routine risk minimisation measures* Routine risk communication: • SmPC Section 4.8 describes frequency of events. • SmPC Section 4.8 describes thromboembolic events may lead to cardiac arrest. • PL Section 2 includes instruction to inform doctor about medical condition. • PL Section 4 describes frequency of events. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 describes to weigh benefit of treatment against risk. Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction *Additional pharmacovigilance activities:* None
Arterial thromboembolic events	*Routine risk minimisation measures* Routine risk communication: • SmPC Section 4.8 describes frequency of events. • SmPC Section 4.8 describes thromboembolic events may lead to cardiac arrest. • PL Section 2 includes instruction to inform doctor about medical condition. • PL Section 4 describes frequency of events. Routine risk minimisation activities recommending specific clinical measures to address the risk:	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction *Additional pharmacovigilance activities:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.4 describes to weigh benefit of treatment against risk. Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None	
Immunogenicity (identified risk for FVII deficiency)	*Routine risk minimisation measures* Routine risk communication: SmPC Section 4.8 describes inhibitory antibody formation. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 describes how treatment should be given in case of severe bleeds. SmPC Section 4.4 describes precautions for suspected antibody formation. Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction *Additional pharmacovigilance activities:* *1.* None
Important potential risk		
Immunogenicity (acquired haemophilia, congenital haemophilia A and B, Glanzmann's thrombasthenia)	Routine risk communication**:** SmPC Section 4.8 describes inhibitory antibody formation. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 describes how treatment should be given in case of severe bleeds. Other risk minimisation measures beyond the Product Information: None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction *Additional pharmacovigilance activities:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures None	
Missing information		
Elderly patients	Routine risk communication: SmPC Section 4.2 and PL Section 2 describe that there is no clinical experience in patients over 65 years. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: None Additional risk minimisation measures None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* *None* *Additional pharmacovigilance activities:* *None*
Pregnant and lactating women	Routine risk communication: SmPC Section 4.6 describes that it is preferably not to use eptacog alfa during pregnancy and why. PL Section 2 includes instruction to ask doctor for advice before use of eptacog alfa. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Single high-dose use (270 µg/kg; in haemophilia A and B with inhibitors)	Routine risk communication: SmPC Section 4.2 and PL Section 2 describe that there is no clinical experience in patients over 65 years.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 describes how treatment should be given in case of severe bleeds. Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None	None *Additional pharmacovigilance activities:* None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication is for the treatment of patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available.

3.1.2. Available therapies and unmet medical need

As the bleeding tendency and severity varies in patients with GT, the treatment demands vary considerably. Mild and moderate bleeding episodes often can be controlled by conservative methods such as local compression, local haemostatic agents (fibrin glue) and antifibrinolytic drugs. However, when such treatment fails, the treatment approach is transfusion of platelets.

Platelet transfusion is the standard therapy to control severe bleeding episodes and to prepare patients for surgical interventions. However, the use of platelet therapy may also be limited by a short platelet shelf-life (5-7 days) and potentially low availability in some hospitals or blood banks, especially if leuco-depleted platelets or leuco-reduced platelets from single donor (if possible HLA compatible) are requested to prevent transfusion reactions.

In GT, refractoriness to platelet transfusion can be considered when platelet transfusions are clinically ineffective in achieving haemostasis. Immune causes of refractoriness include alloimmunisation to human leucocyte antigen (HLA) and/or human platelet antigen (HPA) due e.g. most often to prior exposure from transfusion, pregnancy or transplantation.

The only potentially curative treatment for GT is bone marrow transplantation, and this is only indicated if the bleeds are severe and when the patient is refractory to platelet transfusions

3.1.3. Main clinical studies

Efficacy and safety data to support the extension of the indication in Glanzmann's thrombasthenia (GT) have come from the post-marketing study F7HAEM-3521 (F7GLANZ), also referred to as the Glanzmann's Thrombasthenia Registry (GTR).

There were 218 patients in the registry: 87 (40%) were children (age <12 years), 19 (9%) were adolescents (age 12 to ≤18 years) and 110 (50%) were adults (>18 years). In the registry, 133 patients received treatment which included Novoseven with similar proportions of patients per above mentioned age category (31%, 12% and 56% respectively).

3.2. Favourable effects

The 218 patients in the registry had 1073 admissions for bleeding episodes and/or invasive procedures/surgeries).
The total number of patients in the GTR treated with Novoseven for any admission (bleed or surgery) was as follows:
133 patients with 492 admissions (94 patients with 333 bleeding episode admissions and 77 patients with 159 surgery admissions) received Novoseven either alone (n=62 patients) or in combination with platelets and/or other haemostatic treatments.

In admissions in which treatment with Novoseven was given, efficacy was rated as effective in 79% (262/333) of all bleeding admissions and in 88% (140/159) of all surgical admissions.

In the admissions for bleeding events which were treated only with Novoseven (n=155) or with N7OH (n=110) (thus without platelets), the rate of effective treatment was approximately 80%. In the admissions for surgery which were treated only with Novoseven (n=62) or with N7OH (n=71), the rate of effective treatment was approximately 90%.

Refractory patients
The numbers of patients refractory to platelet transfusions (n=31) according to antibody categories and NovoSeven treatment with rating of haemostatic efficacy were:

Refract POS / AB POS (current indication): 22 patients with 76 admissions.
Efficacy was rated as effective in 72% (26/36) of admissions for bleeds and 95% (38/40) for surgery.
14 patients in 31 admissions were treated only with Novoseven.

Refract POS / AB NEG (covered by proposed modified (indication): 8 patients with 43 admissions.
Efficacy was rated as effective in 74% (23/31) of admissions for bleeds and 67% (8/12 with rest partially effective) for surgery.
4 patients in 12 admissions were treated only with Novoseven.

Refract POS / AB unknown: 1 patient with 7 admissions
Efficacy was rated as effective in all 6 admissions for bleeds and the single admission for surgery.
4 admissions were treated only with Novoseven.

Non-refractory patients

The numbers of patients not refractory to platelet transfusions (n=63) according to antibody categories and NovoSeven treatment with rating of haemostatic efficacy were:

Refract NEG / AB POS: 21 patients with 72 admissions (covered by proposed modified indication). Efficacy was rated as effective in 64% (30/47) of admissions for bleeds and 84% (21/25)for surgery. 6 patients in 12 admissions were treated only with Novoseven.

Refract NEG / AB NEG: 37 patients with 196 admissions (covered by proposed modified indication). Efficacy was rated as effective in 85% (135/159) of admissions for bleeds and 95% (35/37) for surgery. 18 patients in 125 admissions were treated only with Novoseven.

Refract NEG / AB unknown: 5 patients with 10 admissions.
Efficacy was rated as effective in 56% (5/9) of admissions for bleeds and the single admission for surgery. One patient in one admission was treated only with Novoseven.

Overall, the haemostatic efficacy of treatments for bleeding events in which Novoseven was used was rated as effective in 75% of admissions in patients refractory to platelet transfusions and 79% of admissions in patients not known to be refractory.
Similarly, for surgical admissions in which Novoseven formed part of the treatment, haemostatic efficacy was rated as effective 89% in admissions in in patients refractory to platelet transfusions and 90% of admissions in patients not known to be refractory.

Severe bleeds / major surgery

Efficacy in bleeding events treated with Novoseven, was rated as effective in approximately 80% of the 265 admissions for bleeds of moderate severity (ineffective in 3 admissions) and approximately 60% to 70% of the 68 admissions for severe bleeds (ineffective in 1 admission).

Efficacy in surgeries treated with Novoseven, was rated as effective in approximately 90% of the 133 admissions for minor surgeries (ineffective in 2 admissions) and in approximately 70% of the 19 admissions for major surgeries (ineffective in 1 admission).

3.3. Uncertainties and limitations about favourable effects

There are limitations due to the observational nature of the registry data; for example, the reason for a patient to be given a particular therapy is according to physician's choice and open to bias. Within the GTR, meaningful comparisons between treatments are hardly possible as there are no pre-defined comparable subgroups.

Novoseven could be used alone and/or in combination with platelet transfusions and/or other haemostatic therapies such as antifibrinolytic agents (tranexamic acid) resulting in many patient subgroups some of which are very small. The treatment groups/sequences defined by the MAH for the evaluation of efficacy make it difficult to evaluate the efficacy of Novoseven alone or in combination with other treatments. In particular, it is not possible to compare efficacy rates across the different treatment groups treated with Novoseven (alone, with OH and/or platelets) and with the groups treated without Novoseven.

Information on both refractory and antibody status was present for only 88 patients. A minority of patients (31/133 (23.3%)) were known to be refractory to platelet transfusions.

Only 22/133 patients (16.5%) who received Novoseven in the GTR in any treatment combination were Refract POS / AB POS thus few patients were known to have been treated exactly according to the approved indication for Novoseven in GT.

Only 8/133 patients (6%) who received Novoseven in the GTR in any treatment combination were Refract POS / AB NEG corresponding to that part of the proposed modified indication "refractory to platelet transfusions without antibodies to platelets".

Despite the above mentioned concerns, it can be concluded that there is a high rate of haemostatic efficacy with Novoseven with treatment in 64% up to 80% rated as effective for bleeding admissions and 67% up to 95% rated as effective in surgical admissions. In addition, there was no apparent difference in the ratings of haemostatic efficacy in the different subgroups according to treatment combinations (with platelets and/or other haemostatic therapy) or according to refractoriness to platelet transfusions or antibody status.

3.4. Unfavourable effects

In the GTR, in patients treated with Novoseven, 15 adverse events 7 serious and 8 non-serious, were reported in 9 patients. Post-marketing, 53 cases, comprising 77 adverse drug reactions (43 serious and 34 non-serious; have been reported cumulatively up to December 2017 from post-marketing sources within the indication of GT.

There was one serious arterial thromboembolic event of 'Ischaemic stroke'; 9 serious venous thromboembolic events; 4 serious and one non-serious mixed thromboembolic events; 7 serious and 17 non-serious cases of lack of efficacy and 3 reports of serious allergic reactions.

Six of the post-marketing case reports had a fatal outcome. Three of these cases concerned patients with severe haemorrhage, and 2 concerned thromboembolic adverse drug reactions; no information is available on the sixth case.

The risk of thrombotic events as well as the risk of allergic or anaphylactic-type reactions was already covered in Section 4.4. of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

As the GTR provides only observational data there is possible underreporting of adverse events.

Adverse events were reported in 9 patients in the GTR with only 2 or 3 patients per subgroup of refractoriness / antibody status. For the post-marketing reports, information about whether the patients were refractory to platelet transfusions or had antibodies to HLA or to GP IIb - IIIa is available for only 11 of the 53 cases. Of these 11 cases, 3 cases were refractory only, 6 with antibodies (and one "immunised") but not refractory and in one case the patient was refractory and had antibodies.

The post-marketing data on the occurrence of TEE in patients treated with Novoseven show that in a high proportion of these cases there was concomitant therapy with antifibrinolytic agents. However, there was also a confounding factor involved in 7 of these 8 cases.

Furthermore, in post-marketing data only cases of adverse events are reported, it is not known how large the population of GT patients is in which antifibrinolytic agents are used concomitant to Novoseven. There are thus no comparative data in which to assess the frequency of TEE in GT patients treated with Novoseven with or without concomitant antifibrinolytic agents or other additional haemostatic therapy.

While it seems plausible that combined use of Novoseven with antifibrinolytic agents in patients with GT would increase the risk of TEE, no firm conclusion can be drawn from the available data.

However, based on the further analysis of the safety data obtained in the GTR and post-marketing there is no need for additions or changes to the current safety information in the SmPC for Glanzmann's Thrombasthenia patients.

3.6. Effects Table

Table 27: Effects Table for Novoseven (data cut-off: 16 December 2011).

Scale	Definition
Effective[a]	Bleeding stopped/haemostasis achieved for 6 hours or more
Partially effective[b]	Bleeding had decreased substantially but continued
Ineffective[b]	Bleeding was unchanged or worsened
Not possible to evaluate[c]	Not applicable

a) If the treatment is considered effective, it should be entered if bleeding stopped in: 1) <6 hours, 2) 6–24 hours or 3) >24 hours after first dose.

b) For treatment outcomes evaluated as partially effective or ineffective, alternative treatment is to be specified.

c) For treatment outcomes not possible to evaluate, a reason is to be specified.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (GTR)						
haemostatic efficacy	Bleeding admissions in patients refractory to platelet transfusions, in whom adequate haemostasis may not be possible	%	75	NA		See clinical section
haemostatic efficacy	Surgical admissions in patients refractory to platelet transfusions, in whom adequate haemostasis may not be possible	%	89	NA		See clinical section
haemostatic efficacy	Bleeding admissions in patients not refractory to platelet transfusions	%	79	NA		See clinical section
haemostatic efficacy	Surgical admissions in patients not refractory to platelet.	%	90	NA		See clinical section
Unfavourable Effects (GTR)						
thrombotic events	Venous and arterial thrombotic events	NA	10 cases	NA	Including 2 fatal cases	See clinical safety
Anaphylactic-type reactions	Serious allergic reactions	NA	3 cases	NA		See clinical safety

Abbreviations: NA: not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Impaired platelet adhesion and aggregation due to reduced or absent GP IIb – IIIa, as in Glanzmann's thrombasthenia results in inadequate primary haemostasis which leads in particular to mucotaneous bleeding. Recommended treatment for patients with GT experiencing more serious bleeds or undergoing surgery is with platelet transfusions in order to provide functioning platelets to promote establishment of a haemostatic plug. Anti-fibrinolytics and local haemostatic products (e.g. fibrin sealants) are also used. These measures may not be sufficient in patients refractory to platelet transfusions (which may be due to antibodies to GPIIb-IIIa or to HLA) and in such cases the haemostatic effect achieved with rFVIIa can be of major importance.

In the GTR, haemostatic efficacy was rated as effective during bleeding episodes if bleeding stopped or haemostasis was achieved for 6 hours or more and for surgery, "effective" was defined as achieving normal haemostasis, both clinically relevant assessments of efficacy. The combined rates of haemostatic efficacy of treatments which included Novoseven, in patients refractory to platelet transfusions, in whom adequate haemostasis may not be possible, were approximately 75% of bleeding admissions and 89% of surgical admissions. Similar high rates of haemostatic efficacy were also seen in patients not refractory to platelet transfusions: 79% of bleeding admissions and 90% of surgical admissions.

In admissions for bleeding and for surgery (refractory and non-refractory patients not evaluated separately), treatment which included Novoseven but not platelets was rated as effective in 80% and 90% of the admissions respectively. There is thus a high likelihood of Novoseven promoting and contributing to effective haemostasis in patients who are refractory and/or in patients for whom platelets are not readily available. In situations where bleeding is difficult to control, and platelet transfusion is necessary, this may allow some extra time to obtain the platelets.

Few adverse events in Novoseven treated patients were reported in the GTR during the 4.5 years over which data was collected. Most of the reports of adverse events in GT patients from literature and post-marketing sources dated from 2003 up to 2017. In that perspective, 53 cases is not a high number but some of the cases with serious ADRs are striking. In the post-marketing data including serious ADRs from the GTR, there were 14 serious ADRs of thrombotic events in 10 cases which had fatal outcomes in 2 patients, showing that life threatening thrombotic events can co-exist with continued bleeding in patients with GT receiving multiple therapies. The risks of thrombosis associated with use of rFVIIa in various settings (including off-label use) is well known and is an important factor to be taken into consideration in the benefit / risk of treatment with Novoseven in the individual patient. Warning and precautions are reflected accordingly in section 4.4. of the SmPC.

3.7.2. Balance of benefits and risks

Platelet transfusion is the treatment of choice for serious bleeds in patients with Glanzmann's thrombasthenia and this is also stated in the Novoseven SmPC Section 4.2 directly after the GT posology recommendation. However, in patients who are refractory to platelet transfusions, their use will be less effective or ineffective. Matched single donor platelet transfusions may be necessary in patients refractory due to antibodies against GPIIb-IIa or to hHLA but are not immediately available for use in acute situations. It is generally recommended that use of platelet transfusions in patients with GT should be reserved for serious bleeding in order to prevent immunisation which would reduce efficacy in future bleeds. A restrictive approach is also recommended in girls and in women of childbearing age in order to prevent immunisation and formation of anti-platelet antibodies which might result in foetal or neonatal thrombocytopenia. Based on the above considerations, an option for an alternative treatment for any

patient with GT i.e. who is refractory to platelet transfusion and for any GT patient for whom a platelet transfusion is not available is of value in this disorder which can cause severe bleeding which is difficult to control.

The haemostatic effectiveness achieved with treatments using Novoseven and rates at which it was similarly observed in both refractory and in non-refractory patients (about half the patients in the GTR), and in patients with antibodies or patients without antibodies to GPIIb-IIIa or HLA (also about half the patients in the GTR), support the currently approved indication for Novoseven in GT and also support the proposed extension of the indication to non-refractory patients and to patients without antibodies.

The most important ADRs reported with rFVIIa used in the treatment of GT are venous and arterial thrombotic events and disseminated intravascular coagulation which are potentially very serious or even fatal. In the Novoseven SmPC, venous thromboembolic events are listed as uncommon and both arterial thromboembolic events and disseminated intravascular coagulation are listed with a frequency of rare.

The information on adverse events from the 133 patients treated with Novoseven in the GTR does not suggest a different ADR profile or frequencies than currently reflected in the SmPC. There was no sign of a trend towards different rates of adverse events in refractory or non-refractory patients or in patients with or without antibodies but numbers of AEs are too low to draw definite conclusions on this.

There was similar, clinically relevant, haemostatic efficacy in patients refractory or not refractory to platelet transfusions and in patients with or without antibodies to GPIIb-IIIa or HLA. No safety issues have been identified which would preclude extending the indication for treatment with Novoseven in GT patients not refractory to platelet transfusions or without antibodies.

There is also a medical need to avoid, if possible, exposure to platelet transfusions in order to prevent immunisation to platelets.

Based on these considerations it is considered justified that the indication is not restricted to Glanzmann's thrombasthenia patients with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions and reworded as:

Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions or where platelets are not readily available.

3.8. Conclusions

The overall B/R of Novoseven is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by concensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available, based on a prospective observational registry and literature references. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in section 4.8 of the SmPC and in Package Leaflet. The updated RMP version 7.1 has been agreed within this procedure.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion EMEA/H/C/000074/II/0104.