Summary Report of Benefit-Risk Assessment

NOVOEIGHT POWDER AND SOLVENT FOR SOLUTION FOR INJECTION 250 IU/VIAL, 500 IU/VIAL AND 1000 IU/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Turoctocog Alfa
Product Registrant	Novo Nordisk Pharma (Singapore) Pte Ltd
Product Registration Number	SIN16109P, SIN16110P, SIN16111P
Application Route	Abridged evaluation
Date of Approval	01 March 2021

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A INTRODUCTION

Novoeight is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Novoeight can be used for all age groups.

The active substance, turoctocog alfa, is a human recombinant factor VIII which may be used to replace factor VIII deficiency in patients.

Novoeight is available in vials containing 250IU, 500IU and 1000IU of turoctocog alfa as lyophilised powder, co-packaged with 0.9% sodium chloride solution (solvent). Other ingredients in the powder vial are L-Histidine, sucrose, polysorbate 80, sodium chloride, L-methionine, calcium chloride dihydrate and water for injections. Ingredients in the solvent vial are sodium chloride and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, turoctocog alfa, is manufactured at Novo Nordisk US Bio Production Inc. West Lebanon, USA. The drug product, Novoeight Powder and Solvent for Solution for Injection, is manufactured at Novo Nordisk A/S, Gentofte, Denmark. The 0.9% Sodium Chloride Solution is manufactured by Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen. Germany.

Drug substance:
Adequate controls have been presented for the cell banks and raw materials. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance were considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale cultivation batches and multiple subsequent purification batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Impurities including size variants are adequately controlled. The drug substance specifications are established in accordance with Ph. Eur. monograph of Human Coagulation Factor VIII (rDNA) and ICH Q6B. The impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and potency testing is presented.

The stability data presented for turoctocog alfa drug substance were adequate to support the approved storage condition and shelf life. The drug substance is approved for storage at -80^{o}C with a shelf life of 48 months. The packaging is Polypropylene (PE) bulk container with PE stopper made of non-coloured Low Density Polyethylene (LDPE).

Drug product (Novoeight Powder):
The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with Ph. Eur. monograph of Human Coagulation Factor VIII (rDNA) and ICH Q6B. The impurity limits were considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is type I glass vial with a lyophilisation stopper made of type I rubber. The stability data submitted were adequate to support the approved shelf-life of 30 months at 2-8°C with a single period no longer than 9 months at 30°C or a single period no longer than 3 months between 30°C to 40°C. However, once the product has been taken out of the refrigerator, it must not be returned to the refrigerator. The reconstituted drug product is stable at 2-8°C for 24 hours, at 30ºC or up to 40ºC for 4 hours.

Drug product (0.9% Sodium Chloride Solution):
The 0.9% Sodium Chloride Solution is sterilised by terminal sterilisation. The manufacturer is compliant with GMP. Proper validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with USP monograph for Sodium Chloride Injection. The container closure system is type I glass pre-filled syringe. The stability data submitted were adequate to support the approved shelf-life of 60 months at below 30 °C.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of turoctocog alfa in the prevention and treatment of bleeds in patients with severe haemophilia A (FVIII activity ≤1%) was based primarily on 4 pivotal studies and 1 supportive study. Studies 3543 investigated the clinical efficacy of turoctocog alfa in adult and adolescents previously treated patients (PTPs), while Study 3545 was conducted in paediatric PTPs and Study 4028 was conducted in both adult and paediatric PTPs. The supportive study, Study 3568, was an extension trial of studies 3543, 3545, 3600, 3893 or 4015 in adult and paediatric PTPs. Study 3809 was conducted in previously untreated patients (PUPs) who were younger than 6 years old.

Study 3543 was a Phase IIII, multi-centre, open-label, single-arm efficacy and safety trial in adolescent (>12 years old) and adult PTPs with severe haemophilia A and with a documented history of at least 150 exposure days to any other FVIII products. Subjects were enrolled to receive bleeding preventive treatment with turoctocog alfa (20-40 IU/kg every second day or 20-50 IU/kg three times per week adjusted to reach a trough level of ≥0.01 IU/mL) for at least 75 preventive exposure days. In case of acute mild/moderate bleeds, the standard treatment was dosing of turoctocog alfa aiming at a post-infusion turoctocog alfa level of at least 0.50 IU/mL that could be repeated, if needed. For treatment of a severe bleed, doses up to 200 IU/kg per day could be used at the discretion of the investigator.

The primary safety endpoint was immunogenicity as measured by the incidence rate of FVIII inhibitors (≥0.6 Bethesda unit [BU]). The secondary efficacy endpoint for bleeding prevention was the annualised bleed rate (ABR) estimated by the cause of bleed using a Poisson model allowing for over dispersion. The haemostatic response of turoctocog alfa after treatment of acute bleeds was evaluated according to a predefined four-grade scale (none, moderate, good or excellent) and the number of infusions required per bleeding episode. Severe bleeds were

recorded by the investigator while mild/moderate bleeds were monitored by the patient in the patient diary. The haemostatic response of turoctocog alfa during and after surgery was also evaluated in a subgroup of patients who underwent surgical procedures.

A total of 150 male patients with severe haemophilia A were dosed, of whom 22 patients had been previously exposed to turoctocog alfa in an earlier first human dose trial. There were 9 patients included the subgroup who underwent surgery. The median number of exposure days per patient for prevention, treatment of bleeds and surgery was 84.0 days. In terms of demographics and baseline characteristics, the mean age of the population was 28 years (range: 12 to 60 years) and 24 patients were adolescents (12-<18 years). The majority of the patients were White (80.7%) and 13.3% were Asian. A total of 35% of the patients had been on prophylactic regimens prior to trial entry, 39% had been on on-demand treatment regimens and 26% had been on both prophylaxis and on-demand treatment. In the 12 months prior to the start of the study, patients on prophylaxis regimens experienced a mean of 8.9 bleeds/patient/year (range: 0 to 55 bleeds/patient/year) while those on non-prophylaxis treatment regimens had a mean of 2.0 bleeds/patient/year (range: 0 to 18 bleeds/patient/year). Most of the patients (prophylaxis: 54%; on-demand: 73%) received plasma-derived FVIII products before study commencement.

Study 3543 met its primary safety endpoint as no FVIII inhibitors were detected. When used for the prevention of bleeds, treatment with turoctocog alfa resulted in an estimated overall mean ABR of 6.50 bleeds/patient/year (95% CI 5.30 -7.97 bleeds/patient/year), while the mean ABR for adolescents and adults was 5.55 bleeds/patient/year and 6.68 bleeds/patient/year, respectively. When broken down by the cause of bleeding, the estimated mean ABR for spontaneous bleeds was 4.32 bleeds/patient/year (3.15 bleeds/patient/year for adolescents and 4.55 bleeds/patient/year for adults), while the rate of traumatic bleeds was 1.62 bleeds/patient/year (2.07 bleeds/patient/year for adolescents and 1.53 bleeds/patient/year for adults).

A total of 499 acute bleeds were reported during this study. When used in the treatment of acute bleeds, the haemostatic response was rated as excellent for 140 (28.1%) of the bleeds, good for 263 (52.7%) of the bleeds, moderate for 62 (12.4%) of the bleeds, and none for 12 (2.4%) of the bleeds. For the remaining 22 (4.4%) of the bleeds, the haemostatic response was not rated. The success rate for treatment of bleeds was 84.5% (excluding bleeds for which there was no outcome reported). A more conservative approach (considering bleeds for which there was no reported outcome as treatment failures) gave a success rate of 80.8% for treatment of bleeds. Of the 499 reported bleeds, 89.4% were stopped with one or two infusions of turoctocog alfa. The success rate in adolescents was lower than that in the total population (71.7% vs 80.8%) but the trends observed in adolescents were otherwise similar to those in the total population.

Haemostasis was successful in all 9 surgeries (8 major surgeries, 1 minor surgery). The haemostatic response during surgery was rated excellent in 77.8% of the surgeries (7 of 9) and good in the remaining 22.2% of surgeries. After haemostasis had been achieved, the haemostatic response was rated excellent in 66.7% of the cases (6 of 9) and good in the remaining 33.3%.

Summary of Key Efficacy Results (Study 3543) (Full Analysis Set)

	All patients	Adolescent patients	Adult patients
Prevention of bleeds			
N	150	24	126
Estimated mean ABR (bleeds/patient/years) (95% CI)	6.50 (5.30 – 7.97)	5.55 (3.35 – 9.19)	6.68 (5.35 – 8.34)
By cause of bleed			
Spontaneous	4.32 (3.34 – 5.59)	3.15 (1.73 – 5.72)	4.55 (3.43 – 6.02)
Traumatic	1.62 (1.22 – 2.15)	2.07 (1.00 – 4.29)	1.53 (1.13 – 2.08)
Other	0.48 (0.29 – 0.79)	0.33 (0.11 – 1.03)	0.51 (0.30 – 0.87)
Treatment of acute bleeds			
Number of bleeds	499	67	432
Total Haemostatic Response			
Excellent (N, %)	140 (28.1)	20 (29.9)	120 (27.8)
Good (N, %)	263 (52.7)	28 (41.8)	235 (54.4)
Moderate (N, %)	62 (12.4)	18 (26.9)	44 (10.2)
None (N, %)	12 (2.4)	1 (1.5)	11 (2.5)
Missing (N, %)	22 (4.4)	0	22 (5.1)
Haemostatic Response by Type of Surgery			
Surgery Type	Major Surgery	Minor Surgery	Total
Number of Patients	8	1	9
Number of Surgeries (%)	8 (100.0)	1 (100.0)	9 (100.0)
Haemostatic Response during Surgery			
Excellent (N, %)	6 (75.0)	1 (100.0)	7 (77.8)
Good (N, %)	2 (25.0)	0 (0.0)	2 (22.2)
Moderate (N, %)	0 (0.0)	0 (0.0)	0 (0.0)
None (N, %)	0 (0.0)	0 (0.0)	0 (0.0)
Haemostatic Response when haemostasis has been achieved			
Excellent (N, %)	5 (62.5)	1 (100.0)	6 (66.7)
Good (N, %)	3 (37.5)	0 (0.0)	3 (33.3)
Moderate (N, %)	0 (0.0)	0 (0.0)	0 (0.0)
None (N, %)	0 (0.0)	0 (0.0)	0 (0.0)

Study 3545 was a Phase III, multi-centre, open-label, safety and efficacy trial in paediatric PTPs with haemophilia A and at least 50 exposure days to their previous FVIII products. Patients aged <12 years with severe haemophilia A (FVIII ≤1 %) and no inhibitors (≥0.6 BU) were included in the trial. Subjects were administered prophylactic treatment with turoctocog alfa at a dose of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. For all bleeds, the standard treatment was dosing of turoctocog alfa aiming for at least FVIII 0.50 IU/mL with doses up to 150 IU/kg per day at the discretion of the investigator.

Safety was the primary endpoint. The secondary endpoints for bleeding prevention were to evaluate the efficacy of turoctocog alfa in paediatric patients based on ABR. The ABR was estimated in total and by cause of bleed (spontaneous, traumatic or other) using a Poisson

model allowing for overdispersion. The secondary endpoints for the treatment of bleeds were haemostatic response of turoctocog alfa and incidence of re-bleed. Re-bleed was defined as a worsening of the bleeding site conditions after an initial period of improvement, either on treatment or within 72 hours after stopping treatment.

Of the 65 enrolled patients, 2 patients withdrawn before dosing with turoctocog alfa and 3 patients withdrawn after dosing; thus 60 patients completed the trial. The median number of exposure days per patient for prevention and treatment of bleeds was 59.5 days. Of the 63 patients who were dosed, 31 were small children (0 - <6 years) and 32 were older children (6 - <12 years). The trial population consisted of males with a median age of 6 years (range: 1 - 11 years) and a median weight of 21.0 kg (range: 11.7 - 56.0 kg). The majority of the patients were White (84%) with a smaller population of Asian (10%). A total of 76% of the patients had been on prophylactic regimens prior to trial entry and 29% had been on on-demand treatment regimens prior to trial entry. In the 12 months prior to the start of the study, patients on prophylaxis regimens experienced a mean of 6.0 bleeds/patient/year (range: 0.0 to 36.0 bleeds/patient/year) while those on non-prophylaxis treatment regimens had a mean of 2.0 bleeds/patient/year (range: 1.0 to 7.0 bleeds/patient/year). Most of the patients (prophylaxis: 76.2%; non-prophylaxis: 28.6%) received plasma-derived FVIII products before study commencement.

Study 3545 met its primary safety endpoint as no FVIII inhibitors were detected. When used for the prevention of bleeds, treatment with turoctocog alfa resulted in an estimated overall mean ABR was 5.33 bleeds/patient/year (95% CI 3.90-7.28 bleeds/patient/year). The mean ABR was 4.77 (95% CI 3.06 - 7.30 bleeds/patient/year) in the small children (0 - <6 years) cohort and 6.11 (95% CI 3.76 - 9.13 bleeds/patient/year) in the older children (6 to <12 years) cohort. A total of 22 patients (35%) did not experience any bleeds. When broken down by the cause of bleeding, the estimated mean ABR for spontaneous bleeds was 1.69 bleeds/patient/year (0.80 bleeds/patient/year for small children and 2.49 bleeds/patient/year for older children), while the rate of traumatic bleeds was 3.55 bleeds/patient/year (3.93 bleeds/patient/year for small children and 3.21 bleeds/patient/year for older children).

A total of 126 bleeds were reported in 63 patients. When used in the treatment of acute bleeds, the haemostatic response was rated as excellent for 68 (54%) of the bleeds, good for 48 (38%) of the bleeds, moderate for 5 (4%) of the bleeds, and none for 2 (1.6%) of the bleeds. For the remaining 3 (2.4%) bleeds, the haemostatic response was not rated. The success rate (excellent/good) for treatment of bleeds was 94.3% (excluding bleeds for which there was no outcome reported). A more conservative approach (considering bleeds for which there was no reported outcome as treatment failures) gave a success rate of 92.1% for treatment of bleeds. Majority of the bleeds (102 bleeds, 81.0%) were stopped with 1 infusion of turoctocog alfa and 18 bleeds (14.3%) were stopped with 2 infusions. The success rate in older children (89.1%) was lower compared overall population (92.1%) but the trends observed in older children was otherwise similar to those of the total population.

Summary of Key Efficacy Results (Study 3545) (Full Analysis Set)

	Small Children	Older Children	Total
Prevention of Bleeds			
N	31	32	63
Estimated mean ABR (bleeds/patient/years) (95% CI)	4.77 (3.06 - 7.30)	6.11 (3.76 - 9.13)	5.33 (3.90 -7.28)
By cause of bleed			
Spontaneous	0.80	2.49	1.69

	(0.43 – 1.49)	(1.20- 5.17)	(0.94 - 3.03)
Traumatic	3.93	3.21	3.55
	(2.29 – 6.72)	(2.09 – 4.93)	(2.51 – 5.03)
Treatment of Acute bleeds			
Number of bleeds	53 (100.0)	73 (100.0)	126 (100.0)
Total Haemostatic Response			
Excellent (N, %)	31 (58.5)	37 (50.7)	68 (54.0)
Good (N, %)	20 (37.7)	28 (38.4)	48 (38.1)
Moderate (N, %)	1 (1.9)	4 (5.5)	5 (4.0)
None (N, %)	1 (1.9)	1 (1.4)	2 (1.6)
Missing (N, %)	0	3 (4.1)	3 (2.4)

Study 4028 is a single-country, multi-centre, open-label trial conducted to evaluate the clinical efficacy of turoctocog alfa in the treatment of bleeding episodes in Chinese patients. Patients recruited had a documented history of 100 days if above 12 years or 50 exposure days under 12 years to any FVIII concentrates. Patients were treated with on-demand treatment (investigator's choice of dose) or prophylaxis treatment of turoctocog alfa on alternate days or 3 times weekly. A starting dose of 25-50 IU/kg and 20-40 IU/kg once every second day or 25-60 IU kg and 20-50 IU/kg three times weekly were recommended for patients <12 years and those ≥12 years respectively. For treatment of bleeds, investigators determined the individual doses based on recommendations from the World Federation of Haemophilia.

The primary endpoint was the haemostatic effect of turoctocog alfa in treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months/patient). The secondary efficacy endpoint for prophylaxis was the number of bleeds (total bleeds assessed as ABR) during the main phase. The haemostatic response of turoctocog alfa after treatment of acute bleeds was evaluated according to a predefined four-grade scale (none, moderate, good or excellent) and the number of infusions required per bleeding episode. The haemostatic response of turoctocog alfa during and after surgery was also evaluated in a subgroup of patients who underwent surgical procedures.

A total of 68 patients were dosed, comprising 9 small children (0 - <6 years), 33 older children (6 - <12 years), 11 adolescents (12 - <18 years) and 15 adults (≥18 years). Of these, 51 patients were placed on a prophylaxis regimen while 17 patients were on on-demand treatment. A total of 66 patients completed the main phase. The average number of exposure days/patient was 68.4 exposure days. The trial population consisted of male patients, the median age was 11 years (range: 2 to 53 years) with a mean (SD) duration of haemophilia of 11.2 (10.4) years. In the 1 year prior to enrolment in the trial, a total of 40 patients were on prophylaxis at some time point, while 32 patients were on-demand at some time point. The mean ABR during the 1 year prior to the study was 24.6 bleeds/patient/year during prophylaxis regimen and 53.7 bleeds/patient/year during on-demand regimen.

When used for the prevention of bleeds as prophylaxis, treatment with turocotocog alfa resulted in an estimated ABR of 4.7 bleeds/patient/year (95% CI 3.18 - 6.98 bleeds/patient/year) in the main phase. Both small children (4.4 bleeds/patient/year) and older children (4.1 bleeds/patient/year) had a similar ABRs; adolescents had a lower ABR (2.3 bleeds/patient/year) and adults had the highest estimated ABR (10.7 bleeds/patient/year). When broken down by the cause of bleeding, the estimated mean ABR for spontaneous bleeds was 2.53 bleeds/patient/year (2.34 bleeds/patient/year in small children, 2.33 bleeds/patient/year in older children, 1.63 bleeds/patient/year for adolescents and 4.80 bleeds/patient/year for adults), while the rate of traumatic bleeds was 2.06 bleeds/patient/year

(2.05 bleeds/patient/year in small children, 1.58 bleeds/patient/year in older children, 0.70 bleeds/patient/year for adolescents and 5.82 bleeds/patient/year for adults).

When used for the prevention of bleeds as on-demand treatment, treatment with turocotocog alfa resulted in an estimated ABR of 73.2 bleeds/patient/year (95% CI 60.89 - 88.02 bleeds/patient/year) in the main phase. For both small children and adolescents, the ABR was not estimated due to small group size, older children had a lower ABR of 66.0 bleeds/patient/year (95% CI 47.74 - 91.41 bleeds/patient/year) and adults had the highest estimated ABR of 83.8 bleeds/patient/year (95% CI 63.43 - 110.62 bleeds/patient/year).

A total of 611 bleeds were reported in 47 patients, including 48 bleeds in 6 small children, 245 bleeds in 20 older children, 28 bleeds in 6 adolescents and 290 bleeds in 15 adults. When used in the treatment of acute bleeds, the haemostatic response was rated excellent for 65.6%, good for 29.5%, moderate for 4.7% of the bleeds, while there was 1 missing response (0.2%). The success rate (excellent/good) for treatment of bleeds was 95.1% (considering bleeds for which there was no reported outcome as treatment failures). Proportions of the 73 traumatic and 533 spontaneous bleeds with a successful haemostatic response were similar (94.5% and 95.3% successful responses, respectively). Of the total 611 bleeds, 580 bleeds (94.9%) were treated with 1–2 injections from start to stop of the bleed. The results of key secondary endpoints provided supportive evidence on the efficacy.

Haemostasis was successful in all 6 surgeries managed with turoctocog alfa (3 major surgeries, 3 minor surgeries). The haemostatic response during surgery was rated excellent in 50.0% of the surgeries (3 of 6) and good in the remaining 50.0% of surgeries. Haemostatic response to turoctocog alfa after all the 6 surgeries was excellent for 83.3% (5 of 6) and good for 16.7%.

Summary of Key Efficacy Results (Study 4028) (Full Analysis Set)

	Small children (0-< 6 years)	Older children (6 -<12years)	Adolescents (12 - < 18 years)	Adults (≥ 18 years)	Total
Prevention of Bleeds – prophylaxis					
N	8	26	10	7	51
Estimated mean ABR (bleeds/patient/ years) (95% CI)	4.4 (1.71 - 11.14)	4.1 (2.15 - 7.87)	2.3 (0.81- 6.72)	10.7 (5.53- 20.57)	4.7 (3.18 – 6.98)
Spontaneous Estimated mean ABR (bleeds/patient/ years) (95% CI)	2.34 (0.75 – 7.28)	2.33 (1.16 - 4.67)	1.63 (0.55 – 4.86)	4.80 (2.31 – 9.97)	2.53 (1.64 – 3.90)
Traumatic Estimated mean ABR (bleeds/patient/ years) (95% CI)	2.05 (0.83 – 5.03)	1.58 (0.78 – 3.22)	0.70 (0.26 – 1.90)	5.82 (1.99 – 17.05)	2.06 (1.20 – 3.54)
Prevention of Bleeds – on-demand					
N	1	7	1	8	17
Estimated mean ABR (bleeds/patient/ years) (95% CI)	-	66.0 (47.74 - 91.41)	-	83.8 (63.43 – 110.62)	73.2 (60.89 – 88.02)

Treatment of Acute bleeds					
N	9	33	11	15	68
Number of bleeds	48*	245	28	290	611
Excellent	35 (72.9)	156 (63.7)	20 (71.4)	190 (65.5)	401 (65.6)
Good	12 (25.0)	73 (29.8)	8 (28.6)	87 (30.0)	180 (29.5)
Moderate	1 (2.1)	15 (6.1)	-	13 (4.5_	29 (4.7)
None	-	-	-	-	-
Missing	-	1 (0.4)	-	-	1 (0.2)
Total Haemostatic Response, N(%)					
Spontaneous bleeds					
N	33 (100.0)	211 (100.0)	25 (100.0)	264 (100.0)	533 (100.0)
Excellent	25 (75.8)	136 (64.5)	17 (68.0)	174 (65.5)	351 (65.9)
Good	8 (24.2)	61 (28.9)	8 (32.0)	80 (30.3)	157 (29.5)
Moderate	-	14 (6.6)	-	11 (4.2)	25 (4.7)
None	-	-	-	-	-
Missing	-	-	-	-	-
Traumatic bleeds					
N	15 (100.0)	32 (100.0)	3 (100.0)	23 (100.0)	73 (100.0)
Excellent	10 (66.7)	18 (56.3)	3 (100.0)	17 (73.9)	48 (65.8)
Good	4 (26.7)	12 (37.5)	-	5 (21.7)	21 (28.8)
Moderate	1 (6.7)	1 (3.1)	-	1 (4.3)	3 (4.1)
None	-	-	-	-	-
Missing	-	1 (3.1)	-	-	1 (1.4)

*only bleeds treated with turoctog alfa were included

Study 3568 was a supportive extension trial for patients completing studies 3543, 3545, 3600, 3893 or 4015. It was a Phase IIIb, open-label, multi-centre, single-arm trial investigating long-term safety and efficacy of turoctocog alfa in paediatric and adult PTPs with severe haemophilia A without inhibitors. Patients received either a preventive regimen with scheduled preventive infusions (20−50 IU/kg once every second day or 20−60 IU/kg three times weekly [standard prophylaxis dosing regimen]; 40−60IU/kg twice weekly or once every third day [less frequent dosing regimen]) with additional treatment for bleeds or on-demand treatment of bleeds as they occurred and occasionally as preventive treatment (for example, before physical activity). Patients were allowed to switch between preventative regimen and on-demand regimens at the investigator's discretion. Switching was only possible at an assessment visit, surgery visit, dispensing visit or unscheduled visit. Subsequent visits were scheduled 26 ± 2 weeks after prior visits and continued until product is available in the local setting.

The primary safety endpoint was immunogenicity as measured by incidence rate of FVIII inhibitors. The haemostatic response to turoctocog alfa (treatment of bleeds) was evaluated as the secondary objective of the study and the key secondary efficacy endpoint was ABR during the prevention period. The haemostatic response of turoctocog alfa during and after surgery was also evaluated in a subgroup of patients who underwent surgical procedures.

A total of 213 patients were dosed with turoctocog alfa and 130 patients completed the main trial. Of the 207 patients who were on the preventive regimen in the main trial, 194 patients were entirely on prophylaxis. Of the 9 subjects who were on the on-demand regimen, 3 subjects switched to the preventative regimen during the study and were counted in both regimen. The mean total number of exposure days per patient (567.3 days for preventive regimen, 37.4 days for on-demand regimen). The population consisted of male patients who

were divided into 4 age groups: 27 small children (0 to <6 years), 28 older children (6 to <12 years), 23 adolescents (12 to <18 years) and 135 adults (≥18 years). The age is defined as the age when the patient entered the first turoctocog alfa trial. The patients were mostly White (83.1%) with a smaller proportion of Asians (11.3%). A total of 81/200 (40.5%) of the patients had been on prophylactic regimens prior to entering the turoctocog alfa programme, 76/200 (38%) had been on non-prophylaxis treatment regimens and 43/200 (21.5%) had been on both prophylaxis and non-prophylaxis treatment. In the 12 months prior to the start of the study, patients on prophylaxis regimens experienced a mean 7.9 bleeds/patient/year (range: 0 to 55 bleeds/patient/year) while those on non-prophylaxis treatment regimens had a mean of 3.7 bleeds/patient/month (range: 0 to 23 bleeds/patient/month).

Study 3568 met its primary safety endpoint as no FVIII inhibitors were detected. When used for the prevention of bleeds, treatment with turoctocog alfa resulted in an estimated overall ABR was 2.44 bleeds/patient/year (95% CI: 2.06−2.89 bleeds/patient/year) with 1.86 bleeds/patient/year in small children, 2.88 bleeds/patient/year in older children, 1.96 bleeds/patient/year in adolescents and 2.59 bleeds/patient/year in adults. When broken down by the cause of bleeding, the estimated mean ABR for spontaneous bleeds was 1.34 bleeds/patient/year with 0.54 bleeds/patient/year in small children, 0.79 bleeds/patient/year in older children, 1.14 bleeds/patient/year in adolescents and 1.76 bleeds/patient/year in adults. The estimated mean ABR for traumatic bleeds was 1.1 bleeds/patient/year with 1.32 bleeds/patient/year in small children, 2.09 bleeds/patient/year in older children, 0.81 bleeds/patient/year in adolescents and 0.83 bleeds/patient/year in adults. The overall estimated annualised bleeding rate among patients following on-demand regimen was 24.02 bleeds/patient/year (95% CI: 16.90−34.15 bleeds/patient/year).

A total of the 2,173 bleeds were reported in 183 of the 213 patients, haemostatic response was rated as excellent for 1,195 (55.0%) of the bleeds, good for 783 (36.0%) of the bleeds and moderate for 177 (8.1%) of the bleeds. For the remaining 9 (0.4%) bleeds, the haemostatic response was missing (0.4%) and not known for 1 patient. The majority of the bleeds in the FAS (n=213) were spontaneous (58.4%) and 41.6% were caused by trauma; however, for older children, 27.5% were spontaneous and 72.5% were caused by trauma. Of the 2173 bleeds, 1,607 (74.0%) were stopped with 1 injection of turoctocog alfa, 336 (15.5%) were stopped with 2 injections and 116 (5.3%) were stopped with 3 injections.

A total of 14 patients underwent surgery during the trial. The haemostatic response for the 18 major and 3 minor surgeries was rated as “excellent” or “good” both during and after surgery.

Summary of Key Efficacy Results (Study 3568) (Full Analysis Set)

	Small children (0 - < 6 years)	Older children (6-< 12 years)	Adolescents (12- <18 years)	Adults (≥ 18 years)	Total
Prevention of bleeds – preventative regimen					
N	27	28	23	129	207
Estimated mean ABR (bleeds/patient/years) (95% CI)	1.86 (1.12 - 3.07)	2.88 (2.00 - 4.15)	1.96 (1.35 - 2.84)	2.59 (2.06 - 3.25)	2.44 (2.06 - 2.89)
Spontaneous bleeds	0.54 (0.24 -1.18)	0.79 (0.34 -1.82)	1.14 (0.71 - 1.83)	1.76 (1.36 - 2.27)	1.34 (1.07 - 1.68)
Traumatic bleeds	1.32	2.09	0.81 (0.56 - 1.17)	0.83	1.1 (0.91 - 1.33)

	(0.83 - 2.09)	(1.51 - 2.89)		(0.61 - 1.13)	
Prevention of bleeds – On-demand regimen					
N	-	-	1	18	19
Estimated mean ABR (bleeds/patient/years) (95% CI)	-	-	-	24.96 (17.58-35.42)	24.02 (16.90 - 34.15)
Treatment of Acute bleeds					
Number of bleeds	204	331	203	1435	2173
By cause of bleeds					
Spontaneous	59 (28.9)	91 (27.5)	119 (58.6)	999 (69.6)	1268 (58.4)
Traumatic	145 (71.1)	240 (72.5)	83 (40.9)	435 (30.3)	903 (41.6)
Traumatic/Spontaneous	-	-	1 (0.5)	-	1 (0.0)
Not known	-	-	-	1 (0.1)	1 (0.0)
Total Haemostatic Response					
Excellent (N, %)	124 (60.8)	189 (57.1)	73 (36.0)	809 (56.4)	1195 (55.0)
Good (N, %)	62 (30.4)	103 (31.1)	109 (53.7)	509 (35.5)	783 (36.0)
Moderate (N, %)	17 (8.3)	37 (11.2)	19 (9.4)	104 (7.2)	177 (8.1)
None (N, %)	1 (0.5)	1 (0.3)	-	7 (0.5)	9 (0.4)
Missing (N, %)	-	1 (1.3)	2 (1.0)	5 (0.3)	8 (0.4)
Not known (N,%)	-	-	-	1 (0.1)	1 (0.0)

Study 3809 was a Phase III, multi-centre, open-label, safety and efficacy trial conducted in paediatric PUPs under 6 years with severe haemophilia A. Patients were given prophylactic doses starting with 15−60 IU/kg once weekly and gradually increased to 20-50 IU/kg every second day or 20-60 IU/kg two or three times weekly. The trial consists of 2 phases: the main phase including the screening visit (visit 1) and 4 subsequent visits, and an extension phase with a rolling visit schedule consisting of 6 planned visits (including 4 dispensing visits) per year. The primary safety endpoint was the incidence rate of FVIII inhibitors in PUPs. The key secondary efficacy endpoints were the haemostatic efficacy of turoctocog alfa and the ABR.

Of the 59 subjects who were treated with turoctocog alfa, 56 subjects completed the main phase. Patients had a mean age of 10.4 months (range: 0.0 to 42.0 months), a mean height of 71.5 cm (range: 50.0 to 103.0 cm) and weight of 9.2 kg (range: 3.0 to 19.7kg). Most subjects were White (72.9%) with a smaller proportion of Asian subjects (20.3%). At baseline, 34 patients had no inhibitors. For the full analysis set, 51 (86.4%) of patients had at least 50 exposure days and 35 (59.%) had at least 100 exposure days.

For the primary safety endpoint, a total of 24 patients (42.9%) who completed the main phase developed FVIII inhibitors following exposure to turoctocog alfa. High titre inhibitors, defined as a peak titre ≥5 BU, accounted for 15 of the 24 inhibitor cases. When used for the prevention of bleeds, treatment with turoctog alfa resulted in the estimated mean ABR of 5.45 bleed/patient/year (95% CI: 4.07 - 7.30 bleeds/patient/year) in the main phase. Patients treated on-demand regimen had a similar estimated ABR of 4.29 bleeds/patient/year (95% CI: 3.10 - 5.96 bleeds/patient/year) in the main phase. In the inhibitor cohort, patients had an estimated bleeding rate of 6.06 bleeds/patient/year (95% CI: 3.63 - 10.14 bleeds/patient/year).

Overall, 126 bleeds were reported in patients treated with turoctocog alfa using the prophylaxis dose and 94 bleeds in patients treated with on-demand regimen. Majority of the bleeds are spontaneous in both prophylaxis (76.2%) and on-demand (68.1%) regimen. During the main phase, haemostatic response for prophylaxis regimen was rated as excellent for 78 (61.9%) of the bleeds, good for 28 (22.2%) of the bleeds, moderate for 11 (8.7%) of the bleeds, and

none for 1 (0.8%) of the bleeds in patients. The haemostatis response for the on-demand regimen was rated as excellent for 52 (55.3%) of the bleeds, good for 35 (37.2%) of the bleeds and moderate for 5 (5.3%) of the bleeds in patients. Out of the 126 bleeds reported for patients on prophylaxis treatment, 88 (69.8%) were stopped with 1 injection and 22 (17.5%) were stopped with 2 injections of turoctocog alfa. Of the 94 bleeds reported for patients on-demand treatment, 62 (66.0%) were stopped with 1 injection and 15 (16.0) were stopped with 2 injections of turoctocog alfa. Haemostatic response was successful in 106 of 126 (94.1%) bleeds in patients treated with prophylaxis during the main phase and 87 of 94 (92.6%) bleeds in the on-demand regimen (considering bleeds for which there was no reported outcome as treatment failures).

Summary of Key Efficacy Results (Study 3809) (Full Analysis Set)

	Main On-demand	Main Prophylaxis	Total Inhibitor Cohort
Prevention of bleeds			
N	50	56	25
Estimated mean ABR (bleeds/patient/years) (95% CI)	4.29 (3.10- 5.96)	5.45 (4.07- 7.30)	6.06 (3.63- 10.14)
Treatment of acute bleeds			
Number of bleeds	94	126	128
By cause of bleed:			
Spontaneous	64 (68.1)	96 (76.2)	114 (89.1)
Traumatic	29 (30.9)	30 (23.8)	14 (10.9)
Spontaneous/ Traumatic	1 (1.1)	-	-
Total Haemostatic Response			
Excellent (N, %)	52 (55.3)	78 (61.9)	6 (4.7)
Good (N, %)	35 (37.2)	28 (22.2)	13 (10.2)
Moderate (N, %)	5 (5.3)	11 (8.7)	8 (6.3)
None (N, %)	-	1 (0.8)	1 (0.8)
Missing (N, %)	2 (2.1)	8 (6.3)	100 (78.1)

Overall, the studies met their efficacy and safety endpoints. These results adequately support the efficacy of Turoctocog alfa for on-demand treatment and control of bleeding episodes and routine prophylaxis and surgical prophylaxis treatment to reduce the frequency of bleeding episodes in adults and children with haemophilia A.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of turoctocog alfa was supported by safety data derived from 4 Phase I trials and 3 Phase III trials in PTPs. The integrated analysis included 301 patients had experienced a total of 948.9 years of exposure to turoctocog alfa for the prevention and for treatment of bleeds. Within this timeframe, 220 patients had been exposed to turoctocog alfa for ≥18 months including 199 patients from trials in PTPs and 21 PUPs. Safety events from Study 4028 were reported separately.

Summary of Key Safety Findings

	Integrated Trials*		Study 4028	
	N (%)	Events (R)	N (%)	Events (R)
Number of patients	301		68	

Total patient years of exposure	932.1		28.7	
All adverse event	264 (87.7)	1970 (2.11)	35 (51.5)	71 (2.474)
Serious adverse events	80 (26.6)	112 (0.12)	2 (2.9)	3 (0.105)
Adverse events by Severity				
Severe	52 (17.3)	71 (0.08)	1 (1.5)	1 (0.035)
Moderate	150 (49.8)	390 (0.42)	5 (7.4)	6 (0.209)
Mild	239 (79.4)	1508 (1.62)	35 (51.5)	64 (2.23)
Missing	1 (0.3)	1 (0.00)	-	-
Adverse events leading to withdrawal	4 (1.3)	4 (0.00)	-	-
Adverse events leading to death	-	-	-	-

*Studies 3522, 3543, 3545, 3568, 3600, 3809, 3893, 4015

Adverse events (AEs) considered related by the sponsor as reported in the analysis included headache, upper respiratory tract infections and administration site erythema. These were consistent with the AEs seen with other FVIII products. Factor VIII inhibition was observed in Study 3809 conducted in young children (0-6 years) PUPs. The safety profile of turoctocog alfa was observed to be similar between children and adults.

In the integrated analysis, 71 AEs in 55 patients were evaluated by the investigator as possibly or probably related to turoctocog alfa. The main AE was FVIII inhibition (30/71) followed by pyrexia (4/71 events) and injection site erythema (3/71 events). There was 1 serious AE reported in Study 3568 where the patient had an acute myocardial infarction which was assessed by the investigator to be possibly related to turoctocog alfa AE. There were 4 patients who withdrew due to AEs with 2 fatal events. However, neither of these deaths were considered to be related to tutoctocog alfa.

In Study 4028, 2 AEs of acne in 1 of the 68 patients were judged to be possibly or probably related to turoctocog alfa by the investigator. Both AEs were reported to be resolved without any change in dosage. There were no AEs leading to withdrawal and no patients died.

The development of FVIII inhibitors was the most common AE considered probably/possibly related to turoctocog alfa in PUPs, comprising 30 of the 36 related AEs, of which 12 were evaluated as severe by the investigator. The other 6 related AEs included 2 events each of rash and pyrexia, 1 infusion reaction and 1 positive FVIII antibody. No cases were reported in PTP except for 1 subject who eventually tested negative. FVIII inhibition is a known risk in the PUP population, appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

Overall, the safety profile of turoctocog alfa in haemophilia A patients was considered acceptable for the intended population given the disease setting.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutation in the coagulation factor eight (FVIII) gene on the long arm of the X-chromosome. Patients with haemophilia A lack or have a reduced production of FVIII, or they produce biochemically

defective FVIII molecules. With a deficiency or absence of FVIII, the activation of coagulation factor ten (FX) becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. The reduced endogenous FVIII and resultant inability to form a stable clot leads to both spontaneous and trauma related haemorrhages, which may occur anywhere. The standard treatment for patients with haemophilia A is substitution therapy including intravenous administration of high purity, plasma derived FVIII concentrates or recombinant FVIII. Replacement therapy can be provided either as prophylaxis to prevent bleeding episodes, as surgical prophylaxis, or as on-demand treatment of bleeding episodes. Prophylactic therapy instituted early in life (prior to the onset of frequent bleeds) is recommended as optimal therapy for patients with severe haemophilia A.

The efficacy of turoctocog alfa for the treatment of bleeds was consistently demonstrated in the clinical studies based on a high proportion of successful haemostatic responses (>90%) and majority of bleeds requiring only 1 injection from start to stop of bleed. Haemostasis was successful in all surgeries (major and minor) both during and after surgeries. The use of turoctocog alfa as preventative treatment was supported by the consistent ABR across adult population PTP (<6 bleeds/patient/year) except for Study 4028 which might be due to dose titration. Overall, turoctocog alfa was shown to prevent bleedings across different age groups, as well as in treatment naïve and previously exposed paediatric patients with severe haemophilia A . The estimated ABR for small children, older children and adolescents are comparable or lower than the adult population for the individual trials. The overall evidence was adequate to support the indication for treatment and prophylaxis of bleeding in patients with haemophilia A in all age groups.

The safety profile of turoctocog alfa was consistent with the known safety profile of other registered FVIII products. FVIII inhibitor development was an adverse event of special interest for turoctocog alfa, in the clinical studies in PTP no inhibitor development was detected with turoctocog alfa while in PUP the rate of developing FVIII inhibitors was similar to those reported for other FVIII products. This risk has been adequately addressed in the local package insert via relevant warnings and precautions.

Overall, the benefit-risk profile of turoctocog alfa for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) for all age groups was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of turoctocog alfa for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) was deemed favourable and approval of the product registration was granted on 01 March 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

NovoEight®
250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU
powder and solvent for solution for injection

Qualitative and quantitative composition

Each vial contains nominally 250, 500, 1000, 1500, 2000 or 3000 IU human coagulation factor VIII (rDNA), turoctocog alfa.

Each pre-filled syringe contains 0.9% sodium chloride solution.

After reconstitution NovoEight® contains approximately 62.5, 125, 250, 375, 500 or 750 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of NovoEight® is approximately 8,300 IU/mg protein.

Turoctocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 1,445 amino acids with an approximate molecular mass of 166 kDA. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells and prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation.

Turoctocog alfa is a B-domain truncated recombinant human coagulation factor VIII (B-domain consists of 21 amino acids of the wild type B-domain) without any other modifications in the amino acid sequence.

Excipient with known effect
0.31 mmol sodium (7 mg) per ml of reconstituted solution.
For the full list of excipients, see *List of excipients.*

Pharmaceutical form

Powder and solvent for solution for injection.

White or slightly yellow powder or friable mass.

Clear and colourless solution for injection.

Clinical particulars

Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
NovoEight® does not contain Willebrand factor and is not indicated in von Willebrand disease.
NovoEight® can be used for all age groups.

Posology and method of administration

Treatment should be initiated under the supervision of a doctor experienced in the treatment of haemophilia.

Posology

The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal level human plasma) or in International Units (IU) (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity is equivalent to that quantity of factor VIII in one ml normal human plasma.

On-demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

Required units (IU) = body weight (kg) ×desired factor VIII rise (%) (IU/dl) ×0.5 (IU/kg per IU/dl).

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/Type of surgical procedure	**FVIII level required (%) (IU/dl)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12–24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat infusion every 12–24 hours for 3–4 days or more until pain and acute disability are resolved
Life threatening haemorrhages	60–100	Repeat infusion every 8–24 hours until threat is resolved
Surgery		
Minor surgery including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved
Major surgery	80–100 (pre- and postoperative)	Repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl)

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual recommended doses are 20–40 IU of factor VIII per kg body weight every second day or 20–50 IU of factor VIII per kg body weight 3 times weekly. In adults and adolesents (>12 years) a less frequent regimen (40-60 IU/kg every third day or twice weekly) may be applicable. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, demonstrating

different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients.

When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Surgery
There is limited experience of surgery in paediatric patients.

Elderly people
There is no experience in patients > 65 years.

Paediatric population
For long term prophylaxis against bleeding in patients below the age of 12 years, doses of 25–50 IU of factor VIII per kg body weight every second day or 25–60 IU of factor VIII per kg body weight 3 times weekly are recommended. For paediatric patients above the age of 12 years the dose recommendations are the same as for adults.

Method of administration
Intravenous use.

The recommended infusion rate for NovoEight® is 1–2 ml/min. The rate should be determined by the patient's comfort level.

For instructions on reconstitution of the medicinal product before administration, see *Instructions on how to use NovoEight®*.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients.*

Known allergic reaction to hamster proteins.

Special warnings and precautions for use
Hypersensitivity
Allergic type hypersensitivity reactions are possible with NovoEight®. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of NovoEight® immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory test. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitors, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

It is strongly recommended that every time NovoEight® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Excipient related considerations
After reconstitution this medicinal product contains 0.31 mmol sodium (7 mg) per ml of reconstituted solution. To be taken into consideration by patients on a controlled sodium diet.

Cardiovascular event
In patients with existing cardiovascular risk factors, substitiution therapy with FVIII may increase the cardiovascular risk.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with NovoEight®.

Fertility, pregnancy and lactation
Animal reproduction studies have not been conducted with NovoEight®. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, NovoEight® should be used during pregnancy and breast-feeding only if clearly indicated.

Effects on ability to drive and use machines
NovoEight® has no influence on the ability to drive and use machines.

Undesirable effects
Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions has been observed.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with NovoEight®, see *Pharmacodynamic properties*. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre is contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions in clinical trials

System Organ Class	Frequency* in PTPs	Frequency* in PUPs	Adverse reaction
Blood and lymphatic system disorders	Uncommon**	Very common**	FVIII inhibition
Psychiatric disorders	Uncommon		Insomnia
Nervous system disorders	Uncommon		Headache, dizziness, burning sensation
Cardiac disorders	Uncommon		Sinus tachycardia, acute myocardial infarction
Vascular disorders	Uncommon		Hypertension, lymphoedema, hyperaemia
		Common	Flushing, thrombophlebitis superficial
Skin and subcutaneous tissue disorders		Common	Rash, rash erythematous
	Uncommon		Rash, lichenoid keratosis, skin burning sensation
Musculoskeletal and connective tissue disorders	Uncommon		Musculoskeletal stiffness, arthropathy, pain in extremity, musculoskeletal pain
		Common	Haemarthrosis, muscle haemorrhage
Respiratory, thoracic and mediastinal disorders		Common	Cough
General disorders and administration site conditions	Common		Injection site reactions***
		Common	Pyrexia, catheter site erythema
	Uncommon		Fatigue, feeling hot, oedema peripheral, pyrexia
Investigations	Common		Hepatic enzymes increased****
		Common	Anti factor VIII antibody positive
	Uncommon		Heart rate increased
Gastrointestinal		Common	Vomiting

disorders			
Injury, poisoning and procedural complications	Common		Incorrect dose administered
		Common	Infusion related reaction
	Uncommon		Contusion
Product issues		Common	Thrombosis in device

*Calculated based on total number of unique patients in all clinical trials (301), of which 242 were previously treated patients (PTPs) and 59 were previously untreated patients (PUPs).
**Frequency is based on studies with all FVIII products which included patients with severe haemophilia A.
***Injection site reactions include injection site erythema, injection site extravasation and injection site pruritus.
****Hepatic enzymes increased include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase and bilirubin.

Description of selected adverse reactions
During all clinical studies with NovoEight® in previously treated patients, a total of 35 adverse reactions were reported in 23 of 242 patients exposed to NovoEight®. The most frequently reported adverse reactions were injection site reactions, incorrect dose administered and hepatic enzymes increased. Of the 35 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to ≤ 12 years of age, 1 event in 1 out of 24 patients (12 to < 18 years of age) and 32 were reported in 21 out of 155 adults (≥ 18 years).

Paediatric population
In clinical trials involving 63 previously treated paediatric patients between 0 and 12 years of age and 24 adolescents between 12 and 18 years of age with severe haemophilia A no difference in the safety profile of NovoEight® was observed between paediatric patients and adults.

In the trial with previously untreated patients, between 0 and 6 years of age, a total of 36 adverse reactions were reported in 32 of 59 patients exposed to NovoEight®. The most frequently reported adverse reaction was Factor VIII inhibition, see section 4.4. High risk genetic mutations were identified in 91.7% of the overall and 93.3% of the high titre inhibitors. No other factors were significantly associated with inhibitor development.

Overdose
No symptoms of overdose with recombinant coagulation factor VIII have been reported.

Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII.
ATC code: B02BD02.

Mechanism of action
NovoEight® contains turoctocog alfa, a human coagulation factor VIII (rDNA), with a truncated B-domain. This glycoprotein has the same structure as human factor VIII when activated and post-translational modifications that are similar to those of the plasma-derived molecule. The tyrosine sulphation site present at Tyr1680 (native full length), which is important for the binding to von Willebrand factor, has been found to be fully sulphated in the turoctocog alfa molecule. When infused into a haemophilia patient, factor VIII binds to endogenous von Willebrand factor in the patient's circulation. The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. Activated factor VIII acts as a co-factor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of bleeding tendencies.

Clinical efficacy
Four multi-centre, open-labelled, non-controlled trials have been conducted to evaluate the safety and efficacy of NovoEight® in the prevention and treatment of bleeds and during surgery in patients with severe haemophilia A (factor VIII activity ≤ 1%). Three of these trials were performed in previously treated patients and the fourth in previously untreated patients. The trials included 297 exposed patients; 175 adolescents or adult patients without inhibitors from the age of 12 years (≥ 150 exposure days), 63 previously treated paediatric patients without inhibitors below 12 years of age (≥ 50 exposure days) and 59 previously untreated patients below 6 years of age. 188 out of 238 previously treated patients continued into the safety extension trial. Treatment with NovoEight® was shown to be safe and had the intended haemostatic and preventive effect. During an accumulated exposure of more than 54,000 days (corresponding to 342 patient years), no factor VIII inhibitor development was observed in the phase 3a clinical trials in previously treated patients. Of the 3,153 reported bleeds observed in 297 of the patients, 2,794 (88.6%) of the bleeds were resolved with 1-2 infusions of NovoEight®.

Table 3 Consumption of turoctocog alfa and overall success rates in previously treated patients

	Younger children (0 – < 6 years)	Older children (6 – < 12 years)	Adolescents (12 – < 18 years)	Adults (≥ 18 years)	Total
Number of patients	31	32	24	151	238
Dose used for prevention per patient (IU/kg BW)					
Mean (SD)	41.5 (8.1)	38.4 (9.4)	28.5 (9.3)	28.5 (8.3)	31.9 (10.1)
Min; Max	3.4; 196.3	3.2; 62.5	17.4; 73.9	12.0; 97.4	3.2; 196.3
Dose used for treatment of bleed (IU/kg BW)					
Mean (SD)	44.0 (12.6)	40.4 (10.5)	29.3 (10.3)	35.0 (12.3)	36.0 (12.5)
Min; Max	21.4; 193.8	24.0; 71.4	12.4; 76.8	6.4; 104.0	6.4; 193.8
Success rate* %	92.2%	88.4%	85.1%	89.6%	89.2%

BW: Body weight, SD: Standard deviation
*Success is defined as either 'Excellent' or 'Good'.

A total of 30 surgeries were performed in 25 patients of which 26 were major surgeries and 4 were minor. Haemostasis was successful in all surgeries and no treatment failures were reported.

Pharmacokinetic properties
All pharmacokinetic studies with NovoEight® were conducted in previously treated patients with severe haemophilia A (FVIII ≤ 1%). The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

In an international study involving 36 laboratories, the assay performance of NovoEight® in FVIII:C assays was evaluated and compared to a marketed full length recombinant FVIII product. The study showed that comparable and consistent results were obtained for both products and that NovoEight® can be reliably measured in plasma without the need of a separate NovoEight® standard.

The single dose pharmacokinetic parameters of NovoEight® are listed in Table 4 for the clotting assay and Table 5 for the chromogenic assay.

Table 4 Single-dose pharmacokinetics of NovoEight® in patients with severe haemophilia A (FVIII ≤ 1%), clotting assay

Parameter	0 − < 6 years	6 − < 12 years	≥ 12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.004)
AUC ((IU*h)/ml)	9.92 (4.11)	11.09 (3.74)	15.26 (5.77)
CL (ml/h/kg)	6.21 (3.66)	5.02 (1.68)	3.63 (1.09)
$t_{½}$ (h)	7.65 (1.84)	8.02 (1.89)	11.00 (4.65)
V_{ss} (ml/kg)	56.68 (26.43)	46.82 (10.63)	47.40 (9.21)
C_{max} (IU/ml)	1.00 (0.58)	1.07 (0.35)	1.226 (0.41)
Mean residence time (h)	9.63 (2.50)	9.91 (2.57)	14.19 (5.08)

Table 5 Single-dose pharmacokinetics of NovoEight® in patients with severe haemophilia A (FVIII ≤ 1%), chromogenic assay

Parameter	0 − < 6 years	6 − < 12 years	≥ 12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.022 (0.006)	0.025 (0.006)	0.029 (0.006)
AUC ((IU*h)/ml)	12.23 (4.36)	14.37 (3.48)	19.63 (7.73)
CL (ml/h/kg)	4.59 (1.73)	3.70 (1.00)	2.86 (0.94)
$t_{½}$ (h)	9.99 (1.71)	9.42 (1.52)	11.22 (6.86)
V_{ss} (ml/kg)	55.46 (23.53)	41.23 (6.00)	38.18 (10.24)
C_{max} (IU/ml)	1.12 (0.31)	1.25 (0.27)	1.63 (0.50)
Mean residence time (h)	12.06 (1.90)	11.61 (2.32)	14.54 (5.77)

The pharmacokinetic parameters were comparable between paediatric patients below 6 years of age and the paediatric patients from 6 to below 12 years of age. Some variation was observed in the pharmacokinetic parameters of NovoEight® between paediatric and adult patients. The higher CL and the shorter $t_{½}$ seen in paediatric patients compared to adult patients with haemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Preclinical safety data
Non-clinical data reveal no special concern for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Pharmaceutical Particulars
List of excipients
Powder:
Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, water for injection and hydrochloric acid.

Solvent:
Sodium chloride and water for injections.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life
During the shelf life, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months

or
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months.

Once the product has been taken out of the refrigerator, the product must not be returned to the refrigerator. Please record the beginning of storage and the storage temperature on the product carton.

After reconstitution:
Chemical and physical in-use stability have been demonstrated for:
- 24 hours stored at 2°C – 8°C
- 4 hours stored at 30°C, for product which has been kept for a single period no longer than 9 months at room temperature (≤ 30°C)
- 4 hours stored up to 40°C, for product which has been kept for a single period no longer than 3 months at above room temperature (30°C up to 40°C).

From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than as stated above, unless reconstitution has taken place in controlled and validated aseptic conditions.
Any unused reconstituted product stored at room temperature (≤ 30°C) or up to 40°C for more than 4 hours should be discarded.

Special precautions for storage
Store in refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage at room temperature (≤ 30°C) or up to 40°C and storage conditions after reconstitution of the medicinal product, see *Shelf life.*

Nature and contents of container
Each pack of NovoEight® 250–3000 IU powder and solvent for solution for injection contains:
- 1 glass vial (type I) with powder and chlorobutyl rubber stopper
- 1 sterile vial adapter for reconstitution
- Type 1 glass 1 pre-filled syringe of 4 ml solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a syringe cap with a stopper (bromobutyl)
- 1 plunger rod (polypropylene)

Not all strengths are registered or marketed.
Marketing authorisation holder
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

NovoEight® is a trademark owned by Novo Nordisk Health Care AG, Switzerland.

Instructions on how to use NovoEight®

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOEIGHT®.
NovoEight® is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a sodium chloride 9 mg/ml (0.9%) solution. The reconstituted NovoEight® must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject NovoEight®.
You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the NovoEight® package.

Do not use the equipment without proper training from your doctor or nurse.
Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medicine directly into the veins, it is important to **use a clean and germ free (aseptic) technique.** Improper technique can introduce germs that can infect the blood.
Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it is expired. Use a new package instead. The expiry date is printed after 'Expiry' on the outer carton, on the vial, on the vial adapter, and on the pre-filled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

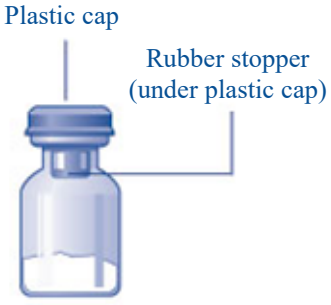
Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

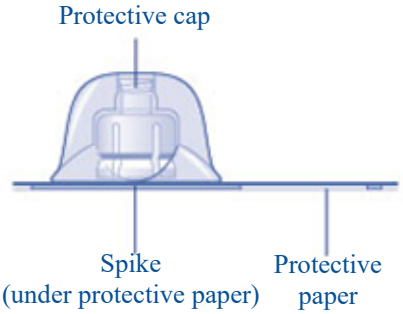
Contents
The package contains:
- 1 vial with NovoEight® powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

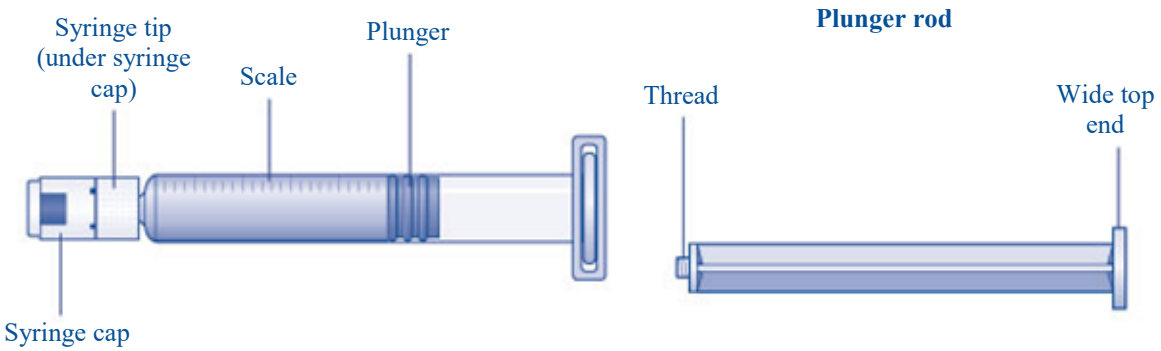
Vial with NovoEight® powder



Vial adapter

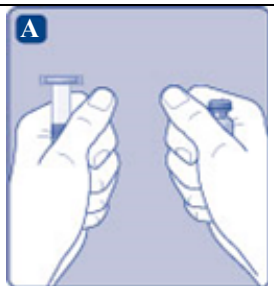


Pre-filled syringe with solvent



1. Prepare the vial and the syringe

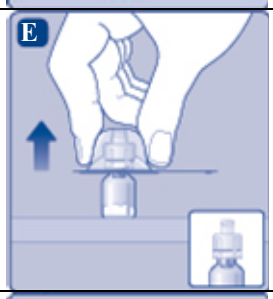
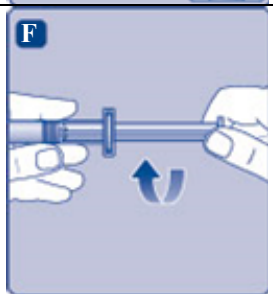
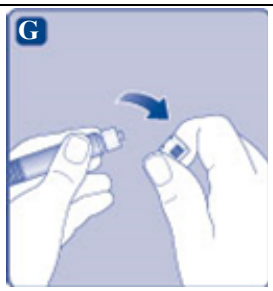
- **Take out the number of NovoEight® packages you need.**
- **Check the expiry date.**
- **Check the name, strength and colour** of the package, to make sure it contains the correct product.
- **Wash your hands** and dry them properly using a clean towel or air dry.
- Take the vial, the vial adapter and the pre-filled syringe out of the carton. **Leave the plunger rod untouched in the carton.**
- **Bring the vial and the pre-filled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands.
- **Do not use any other way to heat** the vial and pre-filled syringe.

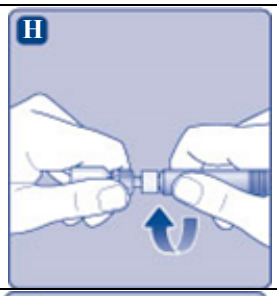
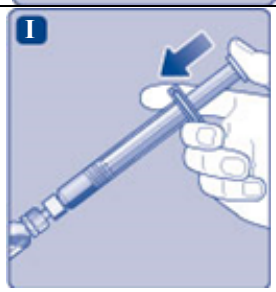


- **Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not use the vial.**
- **Wipe the rubber stopper with a sterile alcohol swab** and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible.
- **Do not touch the rubber stopper with your fingers as this can transfer germs.**

2. Attach the vial adapter

- **Remove the protective paper** from the vial adapter.

If the protective paper is not fully sealed or if it is broken, do not use the vial adapter. **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter, germs from your fingers can be transferred.	
• **Place the vial on a flat and solid surface.** • **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not remove the vial adapter from the vial.**	
• Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter. **Do not lift the vial adapter from the vial** when removing the protective cap.	
3. Attach the plunger rod and the syringe • Grasp the plunger rod by the wide top end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred. • **Immediately** connect the plunger rod to the syringe by turning it clockwise into the plunger inside the pre-filled syringe until resistance is felt.	
• **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks. • **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred. **If the syringe cap is loose or missing, do not use the pre-filled syringe.**	

• **Screw the pre-filled syringe securely** onto the vial adapter until resistance is felt.	
4. Reconstitute the powder with the solvent • **Hold the pre-filled syringe slightly tilted** with the vial pointing downwards. • **Push the plunger rod** to inject all the solvent into the vial.	
• **Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** • **Check the reconstituted solution.** It must be clear to slightly opalescent (slightly unclear). **If you notice visible particles or discolouration, do not use it.** Use a new package instead.	

NovoEight® is recommended to be used immediately after it has been reconstituted. This is because if left, the medicine may no longer be sterile and could cause infections.

If you cannot use the reconstituted NovoEight® solution immediately, it should be used within 4 hours when stored at room temperature or up to 40ºC and within 24 hours when stored at 2°C – 8°C. Store the reconstituted product in the vial.

Do not freeze reconstituted NovoEight® solution or store it in syringes.

Do not store the solution without your doctor's advice.

Keep reconstituted NovoEight® solution out of direct light.

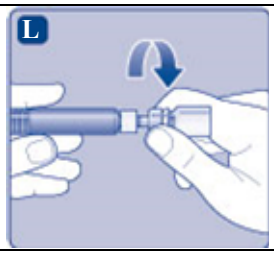
If your dose requires more than one vial, repeat steps **A** to **J** with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.

- **Keep the plunger rod pushed completely in.**
- **Turn the syringe** with the vial upside down.
- **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe.
- **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe.
- **In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.**

If, at any point, there is too much air in the syringe, inject the air back into the vial.

- While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top.
- **Push the plunger rod** slowly until all air bubbles are gone.

- **Unscrew the vial adapter** with the vial.
- **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.



5. Inject the reconstituted solution

NovoEight® is now ready to be injected into your vein.

- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.
- Do not mix NovoEight® with any other intravenous infusions or medicines.

Injecting NovoEight® via needleless connectors for intravenous (IV) catheters

Caution: The pre-filled syringe is made of glass and is designed to be compatible with standard luer lock connections. Some needleless connectors with an internal spike are incompatible with the pre filled syringe. This incompatibility may prevent administration of the medicine and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.

<table>
<tr><td colspan="2">
• Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the reconstituted solution. This should be done right after step J.
• If the CVAD line needs to be flushed before or after NovoEight® injection, use sodium chloride 9 mg/ml solution for injection.
</td></tr>
<tr><td>
Disposal

• After injection, safely dispose of all unused NovoEight® solution, the syringe with the infusion set, the vial with the vial adapter and other waste materials as instructed by your pharmacist.

Do not throw it out with the ordinary household waste.
</td><td>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<tr><td colspan="2">
Do not disassemble the equipment before disposal.
Do not reuse the equipment.
</td></tr>
</table>