EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/71764/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name NovoThirteen

Procedure No. EMEA/H/C/002284/II/0002

Marketing authorisation holder (MAH): Novo Nordisk A/S

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

aPTT	Activated Partial Thromboplastin Time
AUC	area under the plasma activity/concentration-time curve
CI	confidence interval
CL	clearance
C_{max}	maximum drug concentration in serum/plasma
CV%	coefficient of variation
FXIII	Coagulation Factor XIII
GCP	Good Clinical Practice
IU	International Units
IV	Intravenous(ly)
MAH	Marketing Authorisation Holder
MRT	mean residence time
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PT	Prothrombin Time
rFXIII	Recombinant Human Coagulation Factor XIII
SD	Standard Deviation
$T_{1/2}$	half-life
V_{ss}	Volume of distribution at steady state

1. Background information on the procedure

1.1. Requested 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 5 June 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
NovoThirteen	CATRIDECACOG	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
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	II

The MAH applied for an extension of the indication for the treatment of bleeding in children with congenital factor XIII A-subunit deficiency below 6 years of age. Consequently, the MAH proposed the update of section 4.1 of the SmPC. In addition, the MAH proposed to update the posology, safety, efficacy and pharmacokinetics information regarding the patient population below 6 years of age in sections 4.2, 4.8, 5.1 and 5.2 of the SmPC, respectively, and to add a recommendation for the dilution of the reconstituted product for patients less than 24 kg in section 6.6 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 9.0.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0001/2013 on the agreement of a paediatric investigation plan (PIP), corresponding to PIP procedure number EMEA-000185-PIP01-08-M05.

At the time of submission of the application, the PIP EMEA-000185-PIP01-08-M05 was not yet completed.

The PDCO issued a letter on partial compliance for the PIP C2-000185-PIP01-08-M05. Study F13CD-3720 is still ongoing (measure 4 of the PIP; open-label, single-arm, multiple dosing trial to evaluate the safety of monthly replacement therapy with recombinant Factor XIII (rFXIII) in subjects with congenital Factor XIII deficiency).

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.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Joseph Emmerich Co-Rapporteur: Jan Mueller-Berghaus

1.3. Steps taken for the assessment

Submission date:	5 June 2013
Start of procedure:	21 June 2013
Rapporteur's preliminary assessment report circulated on:	30 August 2013
Rapporteur's updated assessment report circulated on:	16 September 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2013
MAH's responses submitted to the CHMP on:	16 October 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 November 2013
PRAC RMP advice and assessment overview adopted by PRAC on:	5 December 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	20 December 2013
Rapporteur's assessment report on the MAH's responses circulated on:	10 January 2014
CHMP opinion:	23 January 2014

2. Scientific discussion

2.1. Introduction

NovoThirteen (catridecacog) is a recombinant DNA- based coagulation FXIII (consisting on a dimer of two FXIII A-subunits) which is identical in structure to the human FXIII A-subunit. NovoThirteen is indicated for the long-term prophylactic treatment of bleeding in patients 6 years and above with congenital factor XIII A-subunit deficiency.

Congenital coagulation factor XIII (FXIII) deficiency is a rare autosomal recessive bleeding disorder with an estimated prevalence of 1 per 2 to 5 million individuals. There are two phenotypic classes of congenital FXIII deficiency, either affecting the A-subunit or the B-subunit of FXIII. Approximately 95 per cent of all known cases of congenital FXIII deficiency are due to mutations in the gene encoding the catalytic A-subunit. In either subtype of FXIII deficiency, the affected individuals have an increased tendency to bleed, with a high rate of severe and life-threatening bleeding episodes such as intracranial haemorrhage.

Diagnosis is based on quantitative FXIII activity measurement and antigen assays. Common clotting assays such as activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT) are normal and cannot be used for the screening. The clot solubility test may also be used (clot is stable for less than 24 hours in case of FXIII deficiency). However, the assay is qualitative, and when performed correctly the test is positive only when the FXIII activity in the sample is close to zero. Differential diagnoses mainly include the other congenital coagulation factor deficiencies: fibrinogen, factors II, V, VII, X, XI, VIII and IX. Antenatal diagnosis is possible if the causal mutations have previously been identified in the family.

Congenital factor XIII deficiency is characterised by haemorrhagic diathesis frequently associated with spontaneous abortions and defective wound healing. Congenital FXIII deficiency can manifest at any age, but diagnosis is often made during infancy. Umbilical stump bleeding manifests in up to 80% of the patients. Other common signs include intracranial haemorrhage (25-30%), soft tissue bleeding, bruising, haemarthroses (20%), and recurrent spontaneous abortions. In most cases, haemorrhages are delayed (12-36hr) after trauma or surgery. Patients may have poor wound healing.

This variation application was submitted to extend the current indication to young children below 6 years of age. In support of this application, the MAH submitted a clinical PK/safety study (F13CD-3760) performed on a paediatric population aged from 1 to 5 years.

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

In accordance with an EMA Paediatric Investigation Plan commitment, a single-dose trial specifically designed to investigate the pharmacokinetics and safety profile of rFXIII in children less than 6 years old with congenital FXIII deficiency (F13CD-3760) was submitted in support of this extension of indication application. Inclusion into a long-term safety follow-on trial (F13CD-3835) was offered to those children who completed the F13CD-3760 trial. Finally, a phase 4, post-marketing observational study is ongoing

as part of the pharmacovigilance plan to substantiate the safety profile of rFXIII after marketing authorisation.

These studies are part of the clinical development programme for recombinant human coagulation factor XIII in patients with congenital FXIII A-subunit deficiency. This included five phase 1 studies (NN1841-3788, F13-1661 and F13-1662, F13-1663 and NN1810-3733) supporting the congenital FXIII deficiency indication, one in patients and four in healthy subjects including a study in Japanese subjects and a bioequivalence study. Therapeutic confirmatory studies comprise a pivotal phase 3 study of monthly administration of 35 IU/kg rFXIII in patients with congenital FXIII A-subunit deficiency (study F13CD-1725). An extension study to the pivotal study is still ongoing (study F13CD-3720).

In addition, two trials have been initiated to evaluate the safety and efficacy of rFXIII in patients undergoing cardiac surgery requiring cardiopulmonary bypass.

The five phase 1 trials were conducted in Europe (NN1841-3788, F13-1661 and F13-1662), US (F13-1663) and Japan (NN1810-3733). The paediatric trial (F13CD-3760) was conducted in UK, US and Israel. Trials F13CD-1725 and F13CD-3720 (Phase 3) were conducted in Europe, US, Canada and Israel.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

Pharmacokinetics in Paediatric Patients with Congenital FXIII Deficiency (study F13CD-3760)

Methods – Analysis of data submitted

The pharmacokinetics of FXIII in paediatric patients (1 to less than 6 years old) with congenital FXIII deficiency was assessed after a single intravenous (IV) dose of rFXIII 35 IU/kg (study F13CD-3760). The phase III study was open-label and PK and safety were evaluated.

The objectives of the study were as follows:

- To characterise the PK of rFXIII in children (1 to less than 6 years old) with congenital FXIII A-subunit deficiency following a single IV dose administration by measuring the area under the concentration vs. time curve ($AUC_{0\text{-}30\ days}$) (IU×h/mL). (Primary objective)
- To investigate additional PK parameters and to evaluate the safety of a single IV dose of rFXIII in children (1 to less than 6 years old) with congenital FXIII A-subunit deficiency. (Secondary objectives).

The patients included were 3 boys and 3 girls, 3 children were Asian, 2 children were White and 1 child was Black/African American. The mean age was 2.7 years.

All children had been on monthly prophylactic treatment with a FXIII containing product (Fibrogammin P/Corifact) prior to inclusion in the study.

The trial included one screening visit, one dosing visit including PK assessments up to 24 hours and four follow-up visits at 7, 14, 21 and 30 days after trial product administration. Blood samples for the PK assessments were drawn pre-dose and at 30 minutes, 24 hours, 7, 14, 21 and 30 days after dosing. The

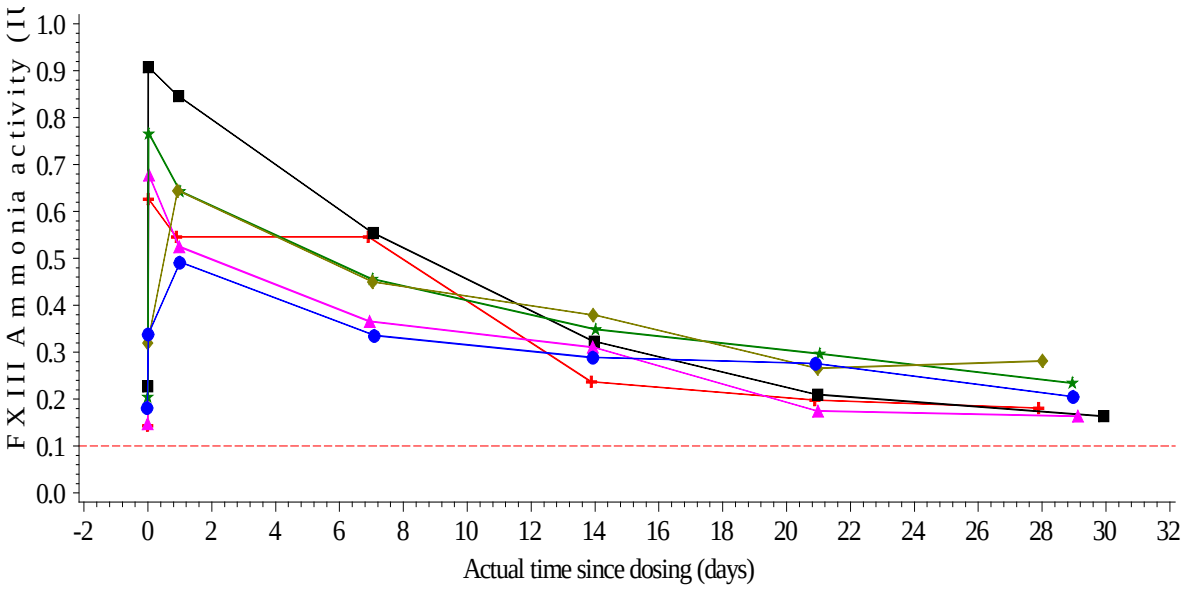
end-of-trial visit was 30 days after dosing where PK and general safety parameters were assessed, including anti-rFXIII antibodies.

The children who completed the present trial were offered participation in a safety extension trial (F13CD-3835: an open-label, single-arm and multiple dose trial on safety and efficacy of monthly replacement therapy with rFXIII in children with congenital FXIII deficiency).

Results

A dose regimen of 35 IU/kg once monthly resulted in increased FXIII activities to well within the normal range at the time of injection and maintaining the activity level above 10% throughout the entire course of the treatment. The mean trough FXIII activity level at 30 days post-dose (0.21 IU/mL) was almost identical to the pre-dose level (0.20 IU/mL). Individual profiles of FXIII activity are presented in Figure 1 below.

After dosing, rFXIII rapidly binds to excess free B-subunit in the blood. As expected, the concentration of free B-subunit in the 6 children decreased after dosing, and then rapidly increased to pre-dose levels (reaching 77% of the pre-dose level during the first 24 h). Importantly, and similar to previous trials, free B-subunit was still measurable in plasma at 30 min following dosing of rFXIII (35 IU/kg), meaning that the B-subunit was not saturated by administration of rFXIII 35 IU/kg.



Original values below LLOQ (0.10 IU/mL) are set equal to ½*LLoQ
The horizontal dashed line indicates LLoQ (0.10 IU/mL)

Figure 1: Individual Profiles of FXIII Activity (IU/mL) in Paediatric Patients with Congenital FXIII Deficiency Following a Single Dose of rFXIII – Trial F13CD 3760

The pharmacokinetic endpoints are summarised in table 2 below. The mean $t_{½}$ of FXIII was 15.8 days (range: 10–25 days) in children. In adult patients (study F13CD-1725), the estimated mean $t_{½}$ was 12 days (range: 7.5–18.5 days). This was consistent with a mean $t_{½}$ of 13 days for healthy subjects (study NN1841-3788). Although the observed difference in $t_{½}$ between children and adults was not statistically significant, a potentially higher $t_{½}$ in children could be anticipated due to the fact that CL and V_{ss} are not perfectly linear with body weight.

The mean CL in children was 0.15 ml/h/kg and consistent with results in healthy adult subjects (NN1841-3788: mean 0.14 mL/h/kg). In contrast, the mean V_{ss} was 89.9 mL/kg in children and hence markedly greater than in healthy adult subjects with endogenous FXIII A subunit and thus a different V_{ss}

(NN1841-3788: mean 48 mL/kg). CL and V_{ss} were not calculated for F13CD-1725 (phase 3, efficacy study).

As expected, the C_{max} was observed at the first assessment at 30 minutes just after the IV dosing. Hereafter, a linear decline over time was observed. The mean C_{max} was 0.69 IU/mL. This C_{max} in children was slightly lower than the C_{max} observed in adult patients (F13CD-1725: mean 0.76 IU/mL) and in healthy subjects (NN1841-3788: mean 0.87 IU/mL).

Table 2: Single Dose Pharmacokinetics for rFXIII in Paediatric Patients with Congenital FXIII Deficiency – Study F13CD-3760

Dose (IU/kg)	N M/F	AUC_{0-30} (h*IU/mL) mean (SD)	$AUC_{0-\infty}$ (h*IU/mL) mean (SD)	C_{max} (IU/mL) mean (SD)	V_{ss} (mL/kg) mean (SD)	CL (mL/h/kg) mean (SD)	$t_{½}$ (h) mean (SD)	MRT (h) mean (SD)
35	3M/3F	250 (31)	359 (61)	0.69 (0.1)	90(31)	0.15(0.0)	378(129)	596 (176)

N = number of patients exposed. M = male; F = female.
PK endpoints derived from Berichrom activity assay.

Systemic exposure was consistent with results from previous clinical trials with rFXIII. The mean $AUC_{0-30\ days}$ was 250 h*IU/mL in children, mean $AUC_{0-28\ days}$ was 248 h*IU/mL in adult patients (F13CD-1725) and mean $AUC_{0-\infty}$ was 301 h*IU/mL in healthy subjects (NN1841-3788).

Some variation in estimates was observed across trials, which is to be expected given the degree of inter-subject variation in pharmacokinetics and the relatively few number of subjects.

Pharmacokinetic parameters were comparable across age groups in the paediatric PK study (F13CD-3760) and in the phase 3 study (F13CD-1725) (see Table 3). In F13CD-1725, C_{max} was 0.75 IU/mL in those aged 6–11 years, 0.67 IU/mL in those aged 12–17 years, and 0.76 IU/mL in those over 18 years.

Trough levels were also comparable across age groups: 0.20 IU/mL in F13CD-3760 and 0.17–0.20 IU/mL in different age groups in the F13CD-1725. A comparable T1/2 was observed across age groups: 15.0 days in F13CD-3760 vs. 11.6–12.4 days in the different age groups in F13CD-1725.

Table 3: Steady state pharmacokinetic parameters for different age groups

Geometric mean (CV, %)	F13CD-3760	F13CD-1725†			F13CD-3720
	1–5 years	6–11 years	12–17 years	18+ years	7-58 years
Patients, *n*	6	9	6	26	23
AUC_{0-28}, IU·h/mL*	248.6 (13)	251.7 (26)	217.1 (19)	245.2 (22)	236.0 (20)
C_{max}, IU/mL	0.67 (21)	0.75 (43)	0.67 (15)	0.76 (21)	0.87 (22)
Trough, IU/mL	0.20 (22)	0.20 (25)	0.17 (28)	0.18 (22)	0.16 (37)
$T_{½}$, days	15.0 (34)	12.4 (21)	11.9 (32)	11.6 (18)	13.6 (25)

The table presents geometrical means (CV %).
*For F13CD-3760, AUC_{0-30} is presented.
†For F13CD-1725, PK calculations were based on a more sparsely sampled curve (three time points vs. six time points for F13CD-3760).
AUC, area under the concentration vs. time curve; C_{max}, maximal measured FXIII activity; CV, coefficient of variance; $T_{1/2}$, terminal half-life.

Results from the F13CD-3720 PK-study are also shown in Table 3. In total, 16 of the 23 patients in the F13CD-3720 trial were part of the F13CD-1725 trial. PK-parameters in F13CD-3720 were comparable to the PK-parameters in F13CD-3760.

An analysis was submitted where all the patients in the three trials have been divided into three age groups (Table 4).

Table 4: Steady state pharmacokinetic parameters for different age groups across trials

Geometric mean (CV)[1]	**1-<6 years**	**6-17 years**		**≥18 years**	
Trial ID	**F13CD-3760**	**F13CD-1725**[3]	**F13CD-3720**	**F13CD-1725**[3]	**F13CD-3720**
N	6	15	3[4]	26	20[4]
Body weight, kg[2]	16 (4)	44 (18)	55 (32)	75 (27)	74 (16)
C_{max}, IU/mL	0.67 (20)	0.71 (38)	0.81 (27)	0.76 (21)	0.88 (22)
$C_{trough, day\ 28}$, IU/mL	0.20[5] (22)	0.19 (26)	0.21 (29)	0.18 (22)	0.15 (42)
$T_{1/2}$, days	15.0 (34)	12.2 (25)	14.1 (16)	11.6 (18)	13.5 (27)
AUC_{0-28}, IU*h/mL	249[6] (12)	237 (25)	258 (22)	245 (23)	232 (21)

[1] CV= coefficient of variation calculated as (SD/mean)*100
[2] Body weight is presented as mean and standard deviation (SD)
[3] Results based on 3 different time points
[4] In total 16 of the 23 patients in the F13CD-3720 trial were also part of the F13CD-1725 trial, 1 in the age group from 6 to 17 years and 15 in the age group ≥18 years
[5] Based on FXIII activities measured 30 days post-dose
[6] Based on $AUC_{0-30days}$

Non-compartmental PK parameters (C_{max}, C_{trough}, AUC0-28/30d, T1/2) were comparable across the three age groups. Post-hoc, pairwise t-tests across the age groups of logtransformed data did not demonstrate any statistically significant differences, when adjusting p values for multiple testing. Additionally, separate ANOVA analyses of each of the parameters, showed no significant differences across the groups (data not shown). The geometric mean half-life ranged from 11.6 to 15.0 days, and the trough FXIII activity levels ranged from 0.15 to 0.20 IU/mL. The geometric mean recoveries were also in the same range; 0.015 (F13CD-1725), 0.013 (F13CD-3760) and 0.020 (F13CD-3720) (IU/mL)/(IU/kg).

Furthermore, mean PK profiles were comparable for the three trials, and C_{max} and C_{trough} values, as well as FXIII exposures (AUC), were constant over time, based on results from patients participating in both the F13CD-1725 and the F13CD-3720 trial.

2.3.3. Pharmacodynamics

No new pharmacodynamic studies were submitted in support to this extension of indication.

2.3.4. Discussion on clinical pharmacology

As indicated in the introduction, the MAH submitted results from the whole clinical development programme. Nevertheless only data submitted in support to this application to extend the use of Novothirteen in children below 6 years of age are assessed in this report.

Although conducted in a limited number of patients, the outcome of F13CD-3760 study allows a reliable characterisation of rFXIII PK parameters in the paediatric patients < 6 years old.

PK data in healthy subjects and patients > 6 years have already been assessed in the frame of the initial marketing authorisation application (MAA). However, it should be reminded that, at the time of initial MAA, questions remained on the full PK assessment of the monthly 35UI/kg dose which is currently approved in patients > 6 years. Indeed, as no PK data with this dosing were formally assessed in patients > 6 years and considering that the available data from study F13CD-3720 showed that the target level of rFXIII (10% of plasma level in non-deficient patients at day 28 post administration) was not achieved in approximately 5 % of patients, the MAH was requested to collect full PK data of the 35IU/kg/month dose in at least 5 patients enrolled in the extension F13CD-3720 study. A separate steady-state PK assessment was performed on a subset of 23 patients, and a full report has been produced.

Based on the whole PK data, the systemic exposure observed in young paediatric patients is considered consistent with that observed in patients > 6 years and supports the claimed dosing scheme of 35UI/kg/month in patients < 6 years old.

2.3.5. Conclusions on clinical pharmacology

The provided PK data supports the claimed dosing scheme in children below 6 years of age.

2.4. Clinical efficacy

No specific efficacy data have been provided for young children < 6 years old as only the phase 3b paediatric PK/safety study (F13CD-3760) – detailed in clinical pharmacology - has been submitted in support of this application. However, all the 6 patients enrolled in this completed study entered an on-going safety and efficacy extension trial (F13CD-3835) where an I.V. dose of 35 IU/kg rFXIII is administered every 4 weeks over a period of a minimum of 1 year. During the follow-up period until 15 January 2013 there were no treatment requiring bleeding episodes among the children enrolled in the F13CD-3835 study. The F13CD-3835 extension trial will continue until Q3 2014 and after that date, the children will be offered participation in the F13CD-3868 PASS study, where follow-up data regarding safety and efficacy will continue to be collected and thus, will be available in the future.

2.4.1. Discussion on clinical efficacy

As the safety/efficacy extension study F13CD-3835 in children below 6 years of age is still on-going, the MAH only provided a brief summary of interim efficacy results. This analysis, which covers data from 6 patients monthly treated with 35 IU/kg of rFXIII, does not seem to identify efficacy issues in the age group of children below 6 years of age. Indeed, no lack of efficacy, no breakthrough bleedings, was observed during this extension study.

Thus, the MAH proposed to extrapolate the efficacy data from adults to children on the basis that paediatric PK profile of NovoThirteen appears comparable between these both populations.

Longer-term efficacy data from the extension study F13CD-3835 in children below 6 years of age, as well as efficacy data from older children (from 6 to 18 years old) through the extension study F13CD-3720 will be submitted by the MAH when the F13CD-3835 and F13CD-3720 clinical study reports will be finalised in May 2015 and October 2016, respectively.

Moreover, it should be noted that congenital coagulation factor XIII (FXIII) deficiency is often diagnosed during infancy, especially in the age range of 0-6 years, when an umbilical stump bleeding or intracranial haemorrhage occur for example. In this context, when the diagnosis is made, the patient should be treated in emergency with FXIII containing products, such as FXIII concentrate or fresh frozen plasma, before initiating a prophylactic treatment which is standard of care. In addition, it should be highlighted

that, in general, young children are more likely to present traumatic bleedings due to frequent falls or bruises. Despite the rarity of the disease and its specific bleeding pattern (incidence much lower than with other coagulation disorders), it appears crucial to collect data on the bleedings treatment in the young children population where treatment requiring bleedings are more likely to occur (i.e. at the time of diagnosis or during daily life). Therefore, the MAH committed to collect information concerning the efficacy and safety of rFXIII for the treatment of breakthrough bleeding during prophylaxis through the observational PASS study NN1841-3868.

2.4.2. Conclusions on the clinical efficacy

In relation to the efficacy of NovoThirteen in the proposed patient population for this extension of indication, the CHMP considered that the provided data are sufficient.

2.5. Clinical safety

2.5.1. Introduction

To support the safety of NovoThirteen in patients below 6 years old, safety data from the paediatric PK/safety study F13CD-3760 performed on 6 patients have been provided by the MAH. However, the MAH did not submit an interim report of the ongoing paediatric extension trial F13CD-3835 but only provided raw safety data.

To further support the findings of study F13CD-3760, an overview of the whole safety data collected throughout the clinical development programme (with a cut-off date of 11 February 2011 for ongoing studies) has been briefly summarised and submitted by the MAH.

Safety data on patients between 1 and 5 years old

F13CD-3760: PK and safety study

The completed F13CD-3760 clinical study evaluated pharmacokinetics and safety in 6 children between 1 and 5 years old who received one single IV dose of rFXIII (at the dose of 35IU/kg).

The patients included were 3 boys and 3 girls, 3 children were Asian, 2 children were White and 1 child was Black/African American. The mean age was 2.7 years (range: 1 to 4 years), the mean weight was 16.4 (from 13.7 to 23.2) kg and the mean height was 98.9 (from 89 to 113) cm.

Adverse events were recorded from dosing until 30 days after dosing. Antibodies against rFXIII were measured pre-dose (Visit 2, 30 minutes prior to dosing) and at Visit 6 (30 days after dosing).

Two mild treatment-emergent adverse events (pyrexia and pain in extremity/arm) were the only reported adverse events following exposure to rFXIII and were considered unlikely related to rFXIII (by the investigator and the MAH):

- An event of pyrexia occurred 29 days after rFXIII exposure with a duration of 2 days in a 1 year old male,
- An event of pain in the arm occurred 4 days after rFXIII exposure with a duration of 68 days in a 3 years old male.

Both children recovered from adverse events. No antibodies against rFXIII were detected.

For 5 of the 6 children, no changes in physical examinations were observed during the trial and 1 scratch on the skin was reported 7 days post-dose in 1 child.

No deaths, serious adverse events or adverse event withdrawals were reported during this period. No probably or possibly rFXIII-related adverse events were reported. No treatment-requiring bleeding episodes occurred.

Overall, no clinically relevant changes have been observed for parameters of haematology, biochemistry and urinalysis.

F13CD-3835: extension study

All the 6 children from F13CD-3760 study completed the trial and continued in the ongoing safety extension trial (F13CD-3835) where an IV dose of 35 IU/kg rFXIII was given every 4 weeks over a period of a minimum of 1 year.

At the time of the 1-year interim report for this extension study (cut-off date: 15 January 2013), 6 children (3 males and 3 females) were enrolled in the study. As of 15 January 2013, no anti-rFXIII antibodies, allergic reactions, embolic or thrombotic events or lack of efficacy were reported. In addition, there were no treatment requiring bleeding episodes as per 15 January 2013. In total, 52 adverse events were reported in 6 subjects. None of the adverse events were assessed by the investigator to be possibly or probably related to rFXIII. All events were reported as recovered. The most frequently reported adverse events in F13CD-3835 were diarrhoea, headache, fall and upper respiratory tract infection.

Out of the 52 adverse events, 2 adverse events from the same female subject were reported as serious adverse events (SAEs), reported at an age of 4 and 5 years of age respectively. The 2 SAEs were from one report of head injury as a result of a fall whilst playing and another report of head injury as a result of falling from a bed. Blood samples were obtained and computerized tomography scan was performed. All laboratory data and investigations were within normal limits. In both reported SAEs, the subject recovered on the next day and was discharged from hospital. All events were assessed to be unlikely related to rFXIII by both investigator and the MAH.

2.5.2. Discussion on clinical safety

In this application to extend the current approved indication to patients aged less than 6 years old, safety data already submitted at the time of the initial marketing authorisation were briefly summarised. In addition safety results on 6 patients aged 1 to 5 years old included in the pharmacokinetics and safety study (F13CD-3760) were provided and did not reveal special safety concerns. An interim report with safety results from the ongoing F13CD-3835 extension study was not provided. However, based on the raw data, the MAH stated that from the period of the supplied data from the F13CD-3835 and F13CD-3720 studies (cut-off dates were 15 January 2013 and 11 February 2011 respectively) until December 2013, no new adverse events or no new late breaking safety information has been reported that would modify the overall safety profile or the benefit-risk balance for rFXIII.

Due to the small volume of NovoThirteen calculated to be administered to paediatric patients weighing less than 24 kg if using the method of administration approved at the time of the initial MAA, the MAH was requested to justify the absence of an appropriate presentation and the proposed modified dilution instruction for children with a body weight of less than 24 kg. More specifically, the MAH was requested to give an estimate on how large the patient population with a body weight of less than 24 kg is and to justify the chosen dilution volume and dilution solution. The justification had to be provided based on the clinical experience obtained with the product thus diluted, on the stability of drug substance in dilution and on the degree of absorption to plastic syringe.

According to the World Federation of Haemophilia Annual Global Survey 2011 (Report on the annual global survey 2011, World Federation of Haemophilia 2012), the global prevalence of Factor XIII congenital deficiency is 1,054. The worldwide prevalence of diagnosed Factor XIII deficiency is estimated at around 1 case per 5 million, but varies from a low of 0.2 per 10 million in South East Asia, to a high of 15 per 10 million in Canada.

Factor XIII A-subunit deficiency is a congenital disease and thereby present at birth, although some patients may not be diagnosed until later in life. No information about birth incidence is available, neither can published information be found about age distribution. However, Factor XIII A-subunit congenital deficiency is an underdiagnosed disease, and is estimated to have a prevalence of 1 in 1- 3 million individuals (Ichinose *et al*, 2005).

The total population in the EU is an estimated 500 million. In 2011, 5.2 million children were born in the EU, thus it can be expected that 2-5 children will be born with Factor XIII A-subunit deficiency per year in the EU area (estimated birth incidence).

A normal weight child would weigh 24 kg when around 7 years of age. In the EU, an estimated 7.5% of the population is below 7 years of age (http://epp.eurostat.ec.europa.eu), thus the patient population with a body weight of 24 kg or below is 7.5% of 500 million, i.e. 37.5 million. Assuming that a maximum of 1 per million of these children below 7 years of age would have Factor XIII A-subunit congenital deficiency that would amount to a prevalence of 37 children with a body weight of 24 kg or less with Factor XIII A-subunit deficiency in the EU area.

Clinical experience with the diluted product

According to protocol and TMM (Trial Material Manual) Appendix B for F13CD-3760 and F13CD-3835 all product must be diluted with 6 ml NaCl prior to administration. Thus the entire 122 exposures (cut-off 30 Sept. 2012) in these 2 trials constitute experience with the further diluted product. No safety concerns have been identified. One event of Infusion site infiltration has been reported as a medication error. A 2 year old 14.5 kg boy experienced an IV infiltration after 0.8 ml of infusion of a planned 1.8 ml dose. The investigator reported the event to be unlikely related to the trial product. This event cannot be attributed to the further dilution of the product. No other reports of medication error have been associated with the product following further dilution.

Stability of drug substance in dilution

The MAH had submitted an in-use stability report during the assessment of the initial MAA. The report included results from an in-use stability study for the rFXIII 2500 IU reconstituted product as well as the product diluted with 0.9% sodium chloride stored 48 hours at 5ºC and 24 hours at 25ºC. The conclusion from the report was that no degradation or change in any parameters is observed during the proposed in-use period 24 hours at 5ºC ± 3ºC or 3 hours at maximum 25ºC.

Degree of absorption to plastic syringe

NovoThirteen is not supplied with a syringe in the carton and the MAH as such does not have any data to support absorption of NovoThirteen to plastic syringes. However, all utensils in the EU have to be CE marked.

Based on the pharmacokinetic data from the clinical trial F13CD-3760 in children below 6 years it is concluded that no dose adjustment is needed as there is no influence of age on the pharmacokinetics of NovoThirteen. No measurable effect from theoretical absorption of protein to the syringe material was observed. Therefore there is no reason to suspect that the further diluted NovoThirteen should have been absorbed to the plastic syringe.

In conclusion, no safety issues have been identified by the MAH in the on-going F13CD-3835 study in patients below 6 years of age.

The MAH has provided sufficient data in order to justify the absence of an appropriate presentation and a proposed dilution instruction for patients with body weight less than 24 kg.

In addition, the CHMP recommended that the applicant should submit the following data regarding the safety concern about medication error related to reconstitution and administration:

- in-use stability data at the start and the end of the approved shelf life of 2 years using at least one batch of "rFXIII 2500 IU diluted".

2.5.3. Conclusions on clinical safety

The safety profile of NovoThirteen in patients aged less than 6 years is considered similar to the safety profile in patients above 6 years of age.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 31 January 2014.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 10.3, the PRAC considers by consensus that the risk management system for CATRIDECACOG (NOVOTHIRTEEN) in the treatment of the proposed/approved indication is acceptable. The following points should be taken into account in the next update:

1- The MAH is requested to update exposure data with the number of patients exposed to rFXIII in the ulcerative colitis NN8717-3946 trial with the next RMP update.

2- The MAH is requested to update the PASS status in section 2.5.5 with the next RMP update.

In addition, the following points need to be addressed by the MAH before CHMP Opinion:

1- The MAH is requested to consider the following modifications:

a. In the Physician Brochure

"The dose volume in millilitres should be calculated based on body weight for each patient using the following formula for patients weighing 24 kg or more*:*
Dose volume in ml = 0.042 x subject bw (kg)"

b. In the Patient Brochure

"NovoThirteen is used to prevent bleeding in patients with congenital factor XIII A-subunit deficiency. Use of NovoThirteen® for other purposes like treatment of breakthrough bleedings in patients with congenital factor XIII A-subunit deficiency is not part of the approved indication.
This is considered off-label use and is not approved by the Health Authority in Europe. This is because the safety and efficacy of NovoThirteen® when used in this way have not been established."

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 6: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Non-neutralising antibodies
Important potential risks	• Neutralising antibodies • Allergic reactions • Embolic and thrombotic events • Drug interaction of rFXIII with rFVII when used outside of the approved indications • Medication error related to reconstitution and administration • Off-label use for management of bleeding
Missing information	Elderly Pregnant and breast-feeding women Patients with renal insufficiency

Pharmacovigilance plans

Table 7: Ongoing and planned studies in the Pharmacovigilance development plan

Study/activity Type, title and category (1–3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
PASS NN1841-3868 Category 2	Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study	Non-neutralising antibodies Neutralising antibodies Allergic reactions Embolic and thrombotic events Lack of efficacy Drug interaction of rFXIII with rFVIIa when used outside of the approved indication off-label use	Planned	December 2018

Study/activity Type, title and category (1–3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
		Medication error related to reconstitution and administration Off-label use for management of bleedings Elderly Pregnant and breast feeding women Patients with renal insufficiency		
Registry PRO-RBDD Category 2	To ensure access to all patients treated with rFXIII, a contractual collaboration has been established with the currently global PRO-RBDD registry. This is a disease registry for patients with congenital FXIII deficiency regardless of treatment.	Neutralising antibodies Allergic reactions Embolic and thrombotic events Lack of efficacy Drug interaction of rFXIII with rFVIIa when used outside of the approved indication off-label use Medication error related to reconstitution and administration Off-label use for management of bleedings Elderly Pregnant and breast feeding women Patients with renal insufficiency	Started	2015
Clinical trial F13CD-3720 Category 3	Investigate safety of monthly replacement therapy with rFXIII in subjects with congenital FXIII deficiency	Neutralising antibodies Allergic reactions Embolic and thrombotic events Lack of efficacy Medication error related to reconstitution and administration Off-label use for management of bleedings Elderly	Started	Oct~~May~~ 2016
Clinical trial F13CD-3835 Category 3	Investigate safety and efficacy of monthly replacement therapy with rFXIII in paediatric subjects with congenital FXIII A-subunit deficiency (safety extension trial to F13CD-3760)	Neutralising antibodies Allergic reactions Embolic and thrombotic events Lack of efficacy Medication error related to reconstitution and administration	Started	Feb~~May~~ 2015~~4~~

Abbreviations: FXIII = coagulation factor XIII; PASS = post-authorisation safety study; PRO-RBDD = Prospective Rare Bleeding Disorder Database; rFVIIa = activated recombinant factor VII; rFXIII = recombinant factor XIII.

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The MAH added a new table for the completed F13CD-3760 study.

Table 8: Completed study F13CD-3760

Study/activity Type, title and category (1–3)	Objectives	Safety concerns addressed	Status	Date of final study report
Clinical trial F13CD-3760 Category 3	A phase 3b trial investigating the pharmacokinetics and safety profile of a single i.v. dose of rFXIII in paediatric (1 to less than 6 years old) subjects with congenital FXIII A-subunit deficiency	Children (<6 years of age)	Completed	14 May 2012

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation Pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 9: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Non-neutralising antibodies	CCDS Sections 4.2 and 4.8 state: • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders." • That frequency of non-neutralising antibodies is common (≥1/100 to <1/10).	None
Neutralising antibodies	CCDS Sections 4.2 and 4.4 state: • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders." • "Inhibitor formation to NovoThirteen® therapy has not been detected in clinical trials. Inhibitors may be suspected in the event of lack of therapeutic response which is observed as bleeding or demonstrated by laboratory findings including FXIII activity that fails to reach expected levels. In the event that inhibitors are suspected analysis for antibodies should be performed. Patients known to have neutralising antibodies to FXIII should not be treated with NovoThirteen® without close monitoring."	None
Allergic reactions	CCDS Sections 4.2, 4.3 and 4.4 state: • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders." • "Contraindication: Hypersensitivity to the active substance or to any of the excipients" • "As NovoThirteen® contains a recombinant protein it may cause allergic reactions including anaphylactic reaction. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. If allergic or anaphylactic-type reactions occur, the administration should be immediately discontinued and further treatment with NovoThirteen® should not be given."	None
Embolic and thrombotic events	CCDS Sections 4.2 and 4.4 state: • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders." • "In case of predisposition to conditions of thrombosis, caution should be exercised due to the fibrin-stabilising effect of NovoThirteen®. A stabilisation of the thrombus might occur, resulting in increased risk of vessel occlusions." • "Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of activated NovoThirteen®. Increased levels of activated NovoThirteen® may increase the risk of thrombosis."	Patient educational material Physician information brochure

	• "The on-demand treatment of acute bleeds or breakthrough bleeds with NovoThirteen® has not been studied in clinical trials. An alternative treatment could be considered in such situations."	
Lack of efficacy	CCDS Sections 4.1, 4.2 and 4.4 state: • "rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency." • "In patients with FXIII deficiency, NovoThirteen® is not effective if used for monthly prophylactic treatment of bleeding in patients with congenital FXIII B-subunit deficiency. FXIII B-subunit deficiency is associated with a much reduced half-life of the administered pharmacologically active A-subunit. The subunit deficiency of patients should be determined prior to treatment by appropriate diagnostic procedures." • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders. The congenital factor XIII A-subunit deficiency should be confirmed by appropriate diagnostics procedures." • "Patients with hepatic impairment have not been studied. NovoThirteen® may not be effective in patients with hepatic impairment if the hepatic impairment is severe enough to result in decreased levels of FXIII B-subunits. FXIII activity levels should be monitored in patients with severe hepatic impairment."	None
Drug interaction of rFXIII with rFVIIa when used outside of the approved indication	The CCDS Sections 4.1, 4.2 and 4.5 state: • "rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency". • "Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders. The congenital factor XIII A-subunit deficiency should be confirmed by appropriate diagnostics procedures." • "There are no clinical data available on interaction between NovoThirteen® and other medicinal products. A potential synergistic effect of combined treatment with NovoThirteen® and rFVIIa in an advanced cardiovascular model in cynomolgus monkey was seen resulting in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds. Based on the nonclinical study it is not recommended to combine NovoThirteen® and rFVIIa."	None

Medication error related to reconstitution and administration	The CCDS Section 4.4 states: "Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of activated NovoThirteen®. Increased levels of activated NovoThirteen® may increase the risk of thrombosis."	Patient educational material Physician information brochure
Off-label use for management of bleedings	The CCDS Sections 4.1 and 4.4 state: • "rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency." • "The on-demand treatment of acute bleeds or breakthrough bleeds with NovoThirteen® has not been studied in clinical trials. An alternative treatment could be considered in such situations."	Patient educational material Physician information brochure
Elderly	The CCDS Section 4.4 states: "There is limited clinical experience in administering NovoThirteen® to elderly patients with congenital FXIII deficiency."	None
Pregnant and breast feeding women	The CCDS Section 4.6 states: • "There are no clinical data on the use of NovoThirteen® in pregnant women. Animal studies are insufficient with respect to reproductive toxicity as NovoThirteen® has not been studied in pregnant animals. The risk to humans is not known. However, based on the therapeutic need the use of NovoThirteen® as a replacement therapy may be considered during pregnancy. It is unknown whether rFXIII is excreted in human breast milk. The excretion of rFXIII drug substance in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoThirteen® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoThirteen® therapy to the mother." • "No effects on reproductive organs have been seen in nonclinical studies. There are no human data on potential effects on fertility."	None
Patients with renal insufficiency	The CCDS Section 4.4 states: "Patients with renal insufficiency requiring dialysis have not been studied in clinical trials."	None

The MAH proposed updates of the Patient and the Physician Brochures in order to minimize the risk of medication error related to the dilution of the vial for small children weighing less than 24 Kg.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s), provided that the requested modifications of the Patient and Physician Brochures are considered before CHMP adoption.

The CHMP endorsed this advice without changes. The requested modifications of the Patient and Physician Brochures were implemented as proposed by the PRAC.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated (new wording underlined, old ~~strikethrough~~). The Package Leaflet has been updated accordingly.

SmPC section 4.1 Therapeutic indications

Long term prophylactic treatment of bleeding in adult and paediatric patients ~~6 years and above~~ with congenital factor XIII A-subunit deficiency.

SmPC section 4.2 Posology and method of administration

Based on the actual concentration of NovoThirteen, the dose volume (in millilitres) to be administered to patients weighing at least 24 kg can be calculated from the formula below:

[…]

Paediatric population

~~The safety and efficacy of NovoThirteen in children less than 6 years have not yet been established.~~

~~No data are available.~~

No dose adjustment is required when NovoThirteen is used in paediatric patients and the dose of 35 IU/kg body weight should be used (see section 5.2 'Paediatric population').

However, if the paediatric patient weighs less than 24 kg, the reconstituted NovoThirteen should be diluted with 6.0 ml of sodium chloride 0.9%, solution for injection to handle the dosing of small children (see section 6.6 'Special precautions for disposal and other handling – Use in the paediatric population').

The dose volume for the reconstituted NovoThirteen diluted with 6.0 ml sodium chloride 0.9% solution for injection can be calculated by using the below formula:

Dose volume in ml = 0.117* x body weight in kilograms.

*The calculation of the correction factor 0.117 is related to the exact quantity of the product and not the nominal value of the product.

Currently available data are described in section 4.8, 5.1 and 5.2.

SmPC section 4.8 Undesirable effects

In clinical trials, NovoThirteen has been administered to ~~51~~56 patients with congenital factor XIII A-subunit deficiency (1043~~924~~ doses of NovoThirteen). 15 patients were between the age of 6 to less than 18 years old and 6 patients were less than 6 years old (total of 393 exposures of NovoThirteen in paediatric subjects (less than 18 years old).

[…]

In clinical studies, adverse reactions were more frequently reported in patients aged from 6 to less than 18 years old than in adults. 4 patients (25%) ~~under~~aged between 6 and 18 years experienced serious adverse reactions in comparison to 3 patients over 18 years (8.5%) that experienced serious adverse reactions. Four cases of non-neutralising antibodies were reported at the start of the treatment in patients from 6 to~~under~~ 18 years of age. 3 of these patients discontinued the study due to the adverse reaction.

In patients below 6 years, no anti-rFXIII antibodies, no thromboembolic adverse events or other safety issues were reported.

SmPC section 5.1 Pharmacodynamic properties

~~The European Medicines Agency has deferred the obligation to submit the results of studies with NovoThirteen in one or more subsets of the paediatric population with factor XIII congenital deficiency.~~Analyses of data from paediatric patients included in clinical trials have not identified differences in treatment response according to age.

Fifteen children between the age of 6 to less than 18 years old and six children less than 6 years old have been treated with NovoThirteen for a total of 393 exposures.

Children above 6 years were investigated through the pivotal phase 3 trial (F13CD-1725) and the on-going extension study (F13CD-3720) assessing the safety of monthly replacement therapy with NovoThirteen.

The 6 patients below 6 years were investigated through a single dose pharmacokinetic phase 3b trial (F13CD-3760) and then, included in the on-going long-term follow-up trial (F13CD-3835) assessing the safety and the efficacy of monthly replacement therapy with NovoThirteen. No treatment requiring bleeding episodes have been detected in patients below 6 years during 8.7 years of cumulative follow-up, representing a total of 116 doses. The suggested dose of 35 IU/kg has shown to be appropriate to provide haemostatic coverage in this young population.

SmPC section 5.2 Pharmacokinetic properties

Paediatric population

In a pharmacokinetic trial 6 children (age 1 to less than 6 years old) with congenital FXIII A-subunit deficiency were exposed to one single i.v. dose of NovoThirteen 35 IU/kg. The mean t½ of FXIII was approximately 15 days (range: 10 to 25 days). In this trial, the mean clearance in children was 0.15 ml/h/kg.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The MAH provided results from a phase 3b single dose PK/safety (F13CD-3760) study performed on 6 patients aged from 1 to 5 years. Moreover, results from the F13CD-3720 PK sub-study performed on patients above 6 years were submitted. Based on the whole PK data, the systemic exposure observed in young paediatric patients is considered consistent with that observed in patients > 6 years and supports the claimed dosing scheme of 35UI/kg/month in patients < 6 years old.

In addition, the MAH provided a brief summary of interim results from the on-going safety/efficacy extension study F13CD-3835 performed in children below 6 years of age. This analysis which covers data from 6 patients monthly treated with 35 IU/kg of rFXIII during one year, did not any identify efficacy issue in the target population. Indeed, no lacks of efficacy or breakthrough bleedings were reported during the observed period.

Therefore, the results of the clinical development programme provide consistent evidence of the haemostatic efficacy of prophylactic treatment with rFXIII in the target population of patients with FXIII A-subunit deficiency.

Uncertainty in the knowledge about the beneficial effects

Due to the rarity of FXIII deficiency, experience with NovoThriteen is still relatively limited in the paediatric population. Longer-term efficacy data from the extension study F13CD-3835 in children below 6 years of age, as well as efficacy data from older children (from 6 to 18 years old) through the extension study F13CD-3720 will be submitted by the MAH when the F13CD-3835 and F13CD-3720 clinical study reports will be finalised in May 2015 and October 2016, respectively.

Risks

Unfavourable effects

Important potential risks with the use of rFXIII comprise neutralising antibodies, thromboembolic events and allergic reactions (see RMP). No clinical safety signals were identified in these respects, and the safety profile of rFXIII supports the use of the drug in the intended target population. The current data do not indicate that the observed transient, low-titre, non-neutralising anti-rFXIII antibodies are of clinical significance. In the 4 patients and the single healthy subject who developed anti-rFXIII antibodies, these were transient, low-titre and non-neutralising antibodies, and no clinical symptoms or changes in C_{trough}

activity levels of FXIII were noted. Furthermore, no thromboembolic events have been reported in trials in patients with congenital FXIII deficiency or in healthy subjects.

The results from the completed paediatric trial (F13CD-3760) provided reassuring safety data also in children less than 6 years.

In addition, raw interim results collected in the ongoing safety/efficacy extension trial F13CD-3835, performed on patients from F13CD-3760 PK study, have been presented by the applicant with the cut-off date of 15 January 2013. This information which covers data from 6 patients monthly treated with 35 IU/kg of rFXIII, does not seem to identify safety issues in the age group of children below 6 years of age. Indeed, no lack of efficacy, no breakthrough bleedings and no related adverse events were observed during this extension study. The related one year interim report was not prepared as study F13CD-3835 was not described as a clinical measure in the PI.

Uncertainty in the knowledge about the unfavourable effects

Based on the PK results from the F13CD-3760 study and the interim efficacy results from the F13CD-3835 study, initial doubts raised on the potential need of dose adjustment in the paediatric population have been addressed for patients below 6 years.

In order to collect missing data on the management of breakthrough bleedings with rFXIII and investigate as much as possible the risk of off-label use in this situation, the MAH planned to collect information concerning the efficacy and safety of rFXIII for the treatment of breakthrough bleeding during prophylaxis through the observational PASS study NN1841-3868 (see RMP).

Benefit-Risk Balance

The results from the completed paediatric trial (F13CD-3760) provided reassuring efficacy and safety data in the children aged less than 6 years.

Based on the provided data, the CHMP considers that the benefit-risk balance in children less than 6 years of age is positive.

4. Recommendations

Final Outcome

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

Variation(s) accepted		**Type**
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	II

Extension of indication to include the treatment of bleeding in children with congenital factor XIII A-subunit deficiency below 6 years of age.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated regarding posology recommendations, as well as safety, efficacy and pharmacokinetics information in this patient population.

In addition, section 6.6 of the SmPC is updated in order to add a recommendation for the dilution of the reconstituted product for patients less than 24 kg. The Package Leaflet is updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, a letter is sent to all expected and actual prescribers of NovoThirteen with an Educational Pack containing the following:

1. Physician brochure
2. Patient brochure

Both documents are to be used as part of an educational plan aiming to minimise risks of medication errors, risk of thromboembolic events due to increased levels of non-proteolytically activated rFXIII in connection with incorrect storage, and risk of off-label use for treatment of breakthrough bleeding. The MAH should ensure harmonisation between terminology used in the brochures and the product information.

The physician brochure should contain the following key elements and item:

- Indication of the product
- The risks of off-label use within FXIII congenital deficiency
- Appropriate diagnostic procedures to confirm FXIII A-subunit deficiency

- Warning of the difference of both posology and concentration between NovoThirteen and other FXIII containing products (The recommended dose of NovoThirteen is 35 IU/kg body weight (bw) once monthly, administered as an intravenous bolus injection. The dose volume in millilitres should be calculated based on body weight for each patient using the following formula: dose volume in ml = 0.042 x subject bw (kg) if bw > 24 kg or dose volume in ml ml = 0.117 x bw (kg) if bw < 24kg).
- Correct handling and the risks associated with mishandling
- Embolic and thrombotic events including the increased risk of vessel occlusion in patients at risk of thrombosis
- What to do in the event of incorrect storage, thrombosis or embolism
- Contraindication of hypersensitivity
- Warning and precautions regarding anaphylaxis
- The importance of collecting safety data and how to enrol patients in the PASS and other registries
- Distribution and use of the patient brochure and the need to ensure that the patient has read and understood the brochure
- Summary of Product Characteristics.

The patient brochure, to be distributed to patients by the prescribers, should contain the following key elements and item:

- Indication of the product
- The risks of off-label use within FXIII congenital deficiency
- How to safely store, handle, reconstitute and administer the product
- The risks associated with incorrect storage and mishandling
- How to recognise the potential side effects (thrombosis and embolism)
- What to do in the event of incorrect storage, thrombosis or embolism
- Package Leaflet.

The Marketing Authorisation Holder must implement this educational plan nationally, prior to marketing. The final content, format and distribution modalities of both documents should be agreed with the national competent authority in each Member State.

• Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.