06 March 2012
EMA/171189/2012

Assessment report for Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names

Pursuant to Article 13 of Commission Regulation EC No 1234/2008

International Non-proprietary Name: somatropin

Procedure number: EMEA/H/A-13/1304

Referral under Article 13 of Commission Regulation EC No 1234/2008

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 14 May 2010, Novo Nordisk submitted an application for an extension of the indications for Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names through a mutual recognition procedure (MRP) type II variation (DK/H/0001/005-007 and 011-016/II/078) with Denmark acting as Reference Member State (RMS). The concerned Member States (CMS) were: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, and the United Kingdom. In May 2011 the Marketing Authorisations of the concerned products were withdrawn in Estonia and in June 2011 the Marketing Authorisations of the concerned products were withdrawn in Latvia.

The applied indication was: "Improvement of growth and body composition in children with Prader-Willi syndrome (PWS) confirmed by appropriate genetic testing".

The type II variation procedure started on 10 June 2010 (90-day extended procedure for a new indication). Since no agreement was reached between the RMS and the CMSs the procedures were referred to CMD(h) by Denmark on 26 January 2011. The CMD(h) 60 day procedure was initiated on 20 February 2011.

Day 60 of the CMD(h) procedure was on 20 April 2011, and since there could be no agreement the procedure was referred to CHMP.

On 20 April 2011, Denmark triggered a referral under Article 13 of Commission Regulation EC No 1234/2008. The CHMP was requested to give its opinion on whether the extension of the indications for medicinal products containing somatropin, Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names should be granted or refused.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Norditropin contains somatropin, which is a human growth hormone produced by recombinant DNA technology (rhGH).

Norditropin is approved in children for growth failure due to growth hormone deficiency, growth failure in girls due to gonadal dysgenesis (Turner syndrome), growth retardation in prepubertal children due to chronic renal disease and growth disturbance in short children born small for gestational age (SGA).

Norditropin is also approved in adults with pronounced growth hormone deficiency in known hypothalamic-pituitary disease.

Norditropin was approved in accordance with Article 8(3) of Directive 2001/83/EC.

The new indication that the company applied for was in children with Prader-Willi syndrome (PWS).

PWS is a genetic disorder. The incidence of PWS is 1 in about 10,000 to 29,000 live births. The diagnosis is based on a genetic test and on clinical findings.

Short stature, mental retardation, behavioural problems, hormonal dysfunctions, poor muscle tone and hyperphagia as well as hypoactivity are among its features. The latter two may lead to childhood obesity. Puberty development is also delayed and often incomplete. Most females with PWS suffer from amenorrhea.

Children with PWS often have concomitant growth hormone deficiency (GHD) (40 to 100%, depending on the provocation test used).

In Europe, two recombinant GH products are approved for the treatment of children with PWS.

The data from the study that were submitted with the application of Novo Nordisk to support the proposed indication were not considered sufficient (open-label, non-controlled and retrospective study) and of good quality (wide range of doses used, height measurements incomplete) by the objecting Member States. Moreover, it was considered inappropriate for the MAH to refer to data from another GH product to claim the same indication since Norditropin was not authorised as a similar biological medicinal product.

2.2. Clinical efficacy

In order to demonstrate efficacy and safety in the applied indication, the application dossier was based on the study GHLiquid-1961. This was a retrospective, observational, open-label, multicentre, multinational study in children with PWS treated with Norditropin off-label for short stature.

The primary objective of the study was to investigate changes in height standard deviation score (HSDS) in response to 1 year of Norditropin treatment in children with PWS (referenced to a PWS population). The secondary objectives were to evaluate in the same population the change in HSDS from start of treatment to last observation during Norditropin treatment (referenced to a PWS population), change in body composition (lean body mass and fat mass), height velocity (HV) and change in HV.

The MAH also discussed data from literature on GH treatment in PWS.

2.2.1. Results

GHLiquid-1961 study

In the GHLiquid-1961 study forty-one (41) children in Europe with genetically documented PWS were enrolled (19 girls and 22 boys). The children were naïve to GH therapy at the time of first dose of Norditropin. There was no restriction on the degree of short stature and the children had to be pre-pubertal at start of treatment. The mean age at inclusion was 3.8 years (min 0.4 years; max 12.2 years). All children were Caucasian.
In this study the dose of Norditropin administered was chosen at the discretion of the physician and adjusted accordingly during the treatment period (the mean dose was 0.03 mg/kg/day).

When standardised to the PWS population, an estimated mean gain in HSDS of 0.9 was obtained after 1 year of Norditropin treatment in short children with PWS. The estimated gain in HSDS was 1.3 to last observation (approximately 6 years). HSDS improved from a baseline mean of -0.3 to 1.1 at last observation.

When standardised to the normal population, an estimated mean gain in HSDS of 0.7 was obtained after 1 year of Norditropin treatment in short children with PWS. The estimated gain in HSDS was 1.1 to last observation. HSDS improved from a baseline mean of -1.8 to -1.2 after 1 year and to -0.7 at last observation (approximately 6 years).

The number of children with an HSDS above -2 was 19 (46%) children at baseline, 27 (66%) children after 1 year of treatment and 35 (85%) children at last observation. Hence, 35 of 41 (85%) children with PWS had a height within the reference range for normal children after Norditropin treatment. The mean HSDS for this subgroup was -0.6 at Year 1 and -0.4 at last observation.

Body composition was improved, with an estimated mean increase in body mass of 9.9% and a corresponding reduction in fat mass of 9.9% after 1 year of Norditropin treatment. Lean body mass increased by 9.1% from baseline to last observation.

The actual lean body mass percentage was 61.8% at baseline, 71.9% at Year 1 and 72.9% at last observation. The actual fat mass percentage was 38.2% at baseline, 28.1% at Year 1 and 27.1% at last observation.

Baseline data on body composition were only available for 11 of the 41 children and hence no definite conclusions could be drawn on body composition based on the GHLiquid-1961 study.

Data from literature and long-term studies

The purpose of the literature review submitted by the MAH was to summarise the clinical experience with GH (from non Novo Nordisk sponsored trials) in the treatment of children with PWS.

Novo Nordisk was of the opinion that the data provided in study GHLiquid-1961 support the data from the literature.

The MAH was of the opinion that the efficacy of long-term GH treatment on growth in children with PWS has been demonstrated and the safety profile of GH treatment in children with PWS is similar to other GH-treated population. In addition to their short stature, patients with PWS often have abnormal body composition, increased fat mass and decreased lean body mass. GH treatment was seen to improve body composition with increases in lean body mass and concurrent reductions in fat mass. GH therapy has a beneficial effect on both height and metabolic disorders in children with PWS and therefore help to reduce associated morbidity and mortality risks (Reus et al. 2011, Brambilla et al. 2010, Angulo et al. 2007).

Since GH products have been used worldwide in PWS children for more than 10 years, the MAH highlighted that clinical experience to date confirms that GH is an efficacious treatment.

During the oral explanation the MAH did not provide any additional data to further support the applied indication. Two experts were also invited by Novo Nordisk who shared their experience with regard to PWS and highlighted the importance of having alternative treatments for this rare disease.

2.2.2. Discussion

The provided study GHLiquid-1961 forming the basis for the application to extend the indication for Norditropin in children with PWS was uncontrolled, open-label and retrospective and not in accordance with the methodological standards for pivotal evidence.

Apart from the aforementioned general deficiency some other aspects of the GHLiquid-1961 study raised concerns to the CHMP namely the validity and the quality of the study results and are summarised below.

In the variation application dossier, the recommended dose from Novo Nordisk for the treatment of short stature and altered body composition in children with PWS was 0.025 to 0.035 mg/kg/day. However, considering requests from some Concerned Member States (CMS) during the CMDh referral, the MAH agreed that the dose recommendation for PWS could be 0.035 mg/kg/day, the same as for other GH products in the same indication.

The CHMP concluded that the rationale for the proposed dose (0.035 mg/kg/day) is still unclear. The recommended dose is not the same as the one studied in the GHLiquid-1961 which was chosen at the discretion of the physician and was on average 0.03 mg/kg/day. In addition, accepting the same recommended dose as for other GH products was not considered appropriate as Norditropin has not shown comparable efficacy and those two products have different dose recommendations for other indications, i.e. Turner syndrome and chronic renal disease (Table 1).

Table 1: Comparison of approved dose range in children across somatropin-containing products (mg/kg/day)

	Norditropin	Genotropin	Omnitrope	Humatrope	Valtropin	Saizen	Nutropin
GHD	0.025 to 0.035	0.025 to 0.035	0.025 to 0.035	0.025 to 0.035	0.025 to 0.035	0.025 to 0.035	0.025 to 0.035
SGA	0.035	0.035	0.035	0.035	N/A	0.035	N/A
Chronic renal disease	0.050	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	Up to 0.05
Turner syndrome	0.045 to 0.067	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	0.045 to 0.050	Up to 0.05
Prader-Willi	N/A	0.035	0.035	N/A	N/A	N/A	N/A

Another point of concern was the fact that based on the wording of the inclusion criteria it was doubtful whether all patients have been included in the study from the respective centres. The inclusion criteria were pre-pubertal children with genetically diagnosed PWS, treated with Norditropin for at least 1 year in the centre. Even children who had only received one dose of Norditropin could be included. No additional information was given by the MAH on the other PWS children for which informed consent was not obtained. The CHMP concluded that given the retrospective design of the study, selection bias cannot be excluded.

The quality of the data was also considered questionable given the fact that basic information such as baseline height was missing in 10% of patients. Height at baseline was only available for 37 patients. IGF-1 SDS at baseline was only available for 28 patients. Data on change in height velocity were not considered valid, as data on pre-trial height measurements were incomplete.
In addition, not only improvement of growth but also improvement of body composition is part of the indication of Norditropin in PWS. Thus body composition would have been a key endpoint. However, the practice of data collection on body composition differed across the three centers. One center did not collect body composition data at all and from the other two centers data were only available in 11 children. Data from 11 out of 41 children were too scarce to draw any conclusion on this endpoint. Height velocity would also have been a valuable endpoint, however no data are available. No data on final adult height were provided.

Overall, the retrospective data collected were insufficient and of poor quality.

2.3. Clinical safety

As already mentioned, in order to prove efficacy and safety, the application dossier was based on the retrospective, observational, open-label, multicentre, multinational study GHLiquid-1961.
In this study safety was assessed by adverse events, HbA1c, IGF-I, haematology, TSH, total T3 and T4, free T3 and T4.

The MAH also discussed safety data from literature on GH treatment in PWS.

2.3.1. Results

GHLiquid-1961

A total of 128 adverse events were reported in 31 (75.6%) children with PWS during Norditropin exposure (mean exposure 4.1 years, range 0.3 to 9.5 years). The majority of events were of mild/moderate severity. The most frequent adverse events were respiratory tract infections which are common in young children (14.6% of children) and scoliosis which is common in PWS (19.5% of children). The yearly frequency of adverse events was 0.8 events/year.

Thirty-three (33.26%) adverse events in 17 (41.5%) children were assessed as probably/possibly related to Norditropin treatment. The most frequent probably/possibly related adverse events were scoliosis (in 8 children, 19.5%) and sleep apnoea (in 3 children, 7.3%).
There were no deaths reported. Two children were withdrawn because of adverse events (central sleep apnoea and enuresis; urinary tract infection and convulsion).
Norditropin treatment led to increases in IGF-I SDS. At baseline, IGF-I SDS was -1.4 and hence below the mean of the reference population. During the first year of treatment, IGF-I SDS increase to +1 and stabilised thereafter on this new higher level. The change in IGF-I SDS from baseline was 2.2 to Year 1 and 2.1 to last observation.
No clinically relevant changes were observed in HbA1c during the exposure period. There were no major changes in other laboratory parameters recorded during the observation period.

Data from literature and long-term studies

The purpose of the literature review submitted by the MAH was to identify safety issues of long-term use of GH (from non Novo Nordisk sponsored trials) in the treatment of children with PWS.

Novo Nordisk was of the opinion that the safety data provided in study GHLiquid-1961 support the data from the literature.

Since GH products have been used worldwide in PWS children for more than 10 years, the MAH highlighted that a small additional clinical study will not provide more safety information than the safety information collected in large company registries like KIGS (Pfizer), NCGS (Genentech), GeNeSiS (Lilly) and NordiNet (NovoNordisk).

2.3.2. Discussion

The safety profile of somatropin-containing products is well known. Sleep apnoea and sudden death have been reported in clinical practice after initiating therapy in patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

No new safety concern emerged from the submitted retrospective data.

2.4. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.5. Overall benefit/risk assessment

Regarding efficacy on the basis of the available data the CHMP concluded that the demonstration of efficacy for Norditropin in PWS is based on limited and unreliable data of apparent poor quality. Only 33 children were included in the primary efficacy analysis and selection bias cannot be excluded due to the design of the study. Moreover, the quality of the data is questionable, as height measurements at baseline were missing in 10% of the subjects. The efficacy of Norditropin on key secondary endpoints such as body composition and height velocity is unknown. Data on final adult heights are not available. Furthermore, a wide range of doses has been used in the retrospective study (mean dose 0.03 mg/kg/day – up to 0.06 mg/kg/day). The CHMP concluded that the rationale for the proposed dose (i.e. 0.035 mg/kg/day) is unclear.

Regarding safety, no new safety concern emerged from the submitted retrospective data.

In conclusion, the data provided by the MAH in particular to support efficacy are insufficient to sustain the extension of indication in PWS.

In addition, it is not considered acceptable to refer to the prospective data obtained with another GH product in order to claim the same indication with the same dose regimen, in view of the legal basis of the marketing authorisation of Norditropin, i.e. Article 8(3) of Directive 2001/83/EC.

3. Overall conclusion

- The Committee considered the notification of the referral triggered by Denmark under Article 13 of Commission Regulation (EC) No 1234/2008.
- The Committee reviewed all available data submitted by the marketing authorisation holder, to support the safety and efficacy of Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names in the applied indication “Improvement of growth and body composition in children with Prader-Willi syndrome (PWS) confirmed by appropriate genetic testing”..
- The Committee is of the opinion that the data submitted by the MAH in particular to support efficacy are considered limited since they are derived from a retrospective, observational, non-comparative study. It is also considered that the data are unreliable and therefore the benefit risk balance of Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names in the applied indication is unfavourable.
- The Committee is also of the opinion that the particulars submitted in support of the application to extend the indications of Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names do not comply with the requirements of a product authorised on the basis of Article 8(3) of Directive 2001/83/EC.

Therefore, the CHMP has recommended the refusal of the variation of the Marketing Authorisations for Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names (see Annex I of the opinion).

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.