# Annex II

## Scientific conclusions and grounds for refusal presented by the EMA

## Scientific conclusions

### Overall summary of the scientific evaluation of Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names (see annex I)

Norditropin contains somatropin which is a human growth hormone produced by recombinant DNA technology that has received marketing authorisation in the European Union through the Mutual Recognition Procedure (MRP). Norditropin was approved in accordance with Article 8(3) of Directive 2001/83/EC.

On 14 May 2010, the MAH submitted a type II variation via the MRP for Norditropin SimpleXx, Norditropin NordiFlex, Norditropin FlexPro and associated names (DK/H/0001/005-007 and 011-016/II/078), to request an extension of the indications.

As the reference and concerned Member States were not able to reach an agreement in respect of the variation, 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 marketing authorisations should be varied to include the indication:

*"Improvement of growth and body composition in children with Prader-Willi syndrome (PWS) confirmed by appropriate genetic testing".*

The referral procedure was initiated on 19 May 2011.

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.

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. Safety was assessed by adverse events, HbA1c, IGF-I, haematology, TSH, total T3 and T4, free T3 and T4.

### Efficacy

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.

Taking into consideration the above mentioned data, the CHMP concluded that 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 the other two GH products approved in the same indication.

The CHMP concluded that the rationale for the proposed dose (i.e. 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.

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.

**Safety**

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). 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.

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.

**Benefit-Risk**

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.

**Grounds for refusal**

Whereas

- 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.

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).