The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

26 June 2003
CPMP/3478/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 7(5) REFERAL

NORDITROPIN

International non-proprietary name (INN): **Somatropin**

BACKGROUND INFORMATION*

Norditropin, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth and by mobilisation of body fat. The first national Marketing Authorisation was granted in Denmark on 28 April 1988 and subsequently in all Member States.

On 2 May 2002, Sweden made a referral to the EMEA under article 7(5) of Commission Regulation 541/95. Sweden considered that the optimal duration of treatment had not been established in the extended indication to include children born small for gestational age (SGA) as applied by the Marketing Authorisation Holders in the variations submitted within the Mutual Recognition Procedure (MRP) and that the limits for catch-up growth to base the initiation of treatment had not been justified, together with safety concerns regarding the increased risk at high doses for development of diabetes mellitus later in life.

The referral procedure started on 30 May 2002. The Rapporteur and Co-Rapporteur appointed were Dr. F. Lekkerkerker and Dr. P. Rossi, respectively. Written explanations were provided by the Marketing Authorisation Holders on 12 July 2002, 6 December 2002 and 25 February 2003.

Based on evaluation of the currently available data and the Rapporteurs' assessment reports, the CPMP considered that the benefit/risk profile of Norditropin in the indication "growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA), with a birth weight and/or length below –2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later" was favourable and therefore adopted an opinion on 19 March 2003 recommending the variation to the Marketing Authorisations in accordance with the ammended Summary of Product Characteristics.

The competent authorites of the Member States will continue to keep the product under regular review.

A list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II, together with the amended Summary of Product Characteristics in Annex III.

The final opinion was converted into a Decision by the European Commission on 26 June 2003.

* **Note**: The information given in this document and Annexes reflect only the CPMP opinion dated 19 March 2003. The Member States competent authorities will continue to keep the product under regular review.

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ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Austria	Novo Nordisk Pharma Gesellschaft mbH Erdbergstr. 52-60/3/16 A-1030 Wien Austria	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Austria	Novo Nordisk Pharma Gesellschaft mbH Erdbergstr. 52-60/3/16 A-1030 Wien Austria	Norditropin SimpleXx	10 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Austria	Novo Nordisk Pharma Gesellschaft mbH Erdbergstr. 52-60/3/16 A-1030 Wien Austria	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Belgium	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Belgium	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	10 mg/1.5	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Belgium	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	15mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1.5 ml,	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1.5 ml,	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin	1,3 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 10
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin PenSet	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Denmark	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin PenSet	8 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Finland	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1.5 ml,	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
Finland	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Finland	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
France	Novo Nordisk France Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin SimpleXx	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
France	Novo Nordisk France Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
France	Novo Nordisk France Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
France	Novo Nordisk Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin	1,3 mg	Powder and solvent for solution for injection	Subcutaneous	Cartridge	1 and 10
France	Novo Nordisk Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1
France	Novo Nordisk Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin PenSet	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
France	Novo Nordisk Pharmaceutique S.A. Le Palatin 30 rue de Valmy La Défense 12 92936 Paris la Défenseé France	Norditropin PenSet	8 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Germany	Novo Nordisk Pharma G.m.b.h. Brücknerstrasse 1 55127 Mainz GERMANY	Norditropin SimpleXx	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
Germany	Novo Nordisk Pharma G.m.b.h. Brücknerstrasse 1 55127 Mainz GERMANY	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3, and 5
Germany	Novo Nordisk Pharma G.m.b.h. Brücknerstrasse 1 55127 Mainz GERMANY	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	15mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin	1,3 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 10

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Greece	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	8 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 10
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Ireland	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	8 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 10
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Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	4 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Italy	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin PenSet	8 mg	Powder and solvent for solution for injection	Subcutaneous	Vial	1 and 6
Luxembourg	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	5 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Luxembourg	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	10 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Luxemburg	Novo Nordisk Pharma SA Bd International 55 1070 Brussels Belgium	*Norditropin SimpleXx*	15 mg/1.5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Netherlands	Novo Nordisk Farma Flemingweg 18 2408 AV Alphen a/d Rijn Netherlands	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Netherlands	Novo Nordisk Farma Flemingweg 18 2408 AV Alphen a/d Rijn Netherlands	Norditropin SimpleXx	10 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Netherlands	Novo Nordisk Farma Flemingweg 18 2408 AV Alphen a/d Rijn Netherlands	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Portugal	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
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Portugal	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Spain	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package Size
Spain	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Spain	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Sweden	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd Denmark	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Sweden	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd Denmark	Norditropin SimpleXx	10 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
Sweden	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd Denmark	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
United Kingdom	Novo Nordisk Ltd. Broadfield Park Brighton Road West Sussex RH11 9RT UNITED KINGDOM	Norditropin SimpleXx	5 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
United Kingdom	Novo Nordisk Ltd. Broadfield Park Brighton Road West Sussex RH11 9RT UNITED KINGDOM	Norditropin SimpleXx	10 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5
United Kingdom	Novo Nordisk Ltd. Broadfield Park Brighton Road West Sussex RH11 9RT UNITED KINGDOM	Norditropin SimpleXx	15 mg/1,5 ml	Solution for injection	Subcutaneous	Cartridge	1, 3 and 5

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF NORDITROPIN AND RELATED NAMES (SEE ANNEX I)

Norditropin, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat.

The variations submitted by the MAHs via the mutual recognition procedure were a proposal to extend the indication to include children born small for gestational age (SGA).

The RMS (Denmark) considered the variation approvable. A notification for referral according to Article 7(5) of Commission Regulation EC No. 541/95 was submitted by Sweden on 2 May 2002 based on concerns that the optimal duration of treatment had not been established and that the limits for catch-up growth to base the initiation of treatment had not been justified, together with safety concerns regarding the increased risk at high doses for development of diabetes mellitus later in life.

On 30 May 2002, the CPMP asked the MAHs to provide data on the optimal age for initiating treatment and duration of GH therapy in SGA children, additional benefits besides increased height, as well as short-term and long-term consequences of treatment.

0 Efficacy

The clinical studies and published literature submitted demonstrate that the use of Norditropin is associated with improvements in predicted height SDS. However, there were insufficient data on (near) final height. Thus, no definite conclusion on the efficacy in the treatment of children born SGA could be reached. On the request of the CPMP, a meta-analysis was performed on patients that reached (near) final height.

This meta-analysis included 56 patients and provided important insights of the benefit of Norditropin for final height improvement in SGA children. The meta-analysis demonstrated a mean increase in height SDS of 1.90 for the 0.033 mg/kg/day dose (1.49-2.30 95% confidence intervals) and 2.19 SDS for the 0.067 mg/kg/day dose (1.85-2.53 95% confidence interval).

Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

The major issues discussed during the procedure were related to the patient population, the age for start of treatment, as well as posology and duration of treatment.

The criteria for the patient population were decided to be height SDS of <-2.5 and a HV SDS of < 0 during the last year. A starting age of 4 years was accepted by the CPMP because normal catch-up growth will occur before the age of 4 years.

The CPMP was of the opinion that the limited data in patients near puberty should lead to the advice not to initiate treatment in SGA patients near the onset of puberty.

Non-responders, expressed as patients with a height gain below the expected, should stop treatment for the lack of efficacy after the first year of treatment if the height velocity SDS is below + 1. Treatment should be stopped if the height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Safety

The data presented in the patient population does not support the existence of major unexpected risks during treatment.

The incidence of drug-related adverse events was low. The most frequently reported adverse events represented common childhood infections (viral infections, otitis media, pharyngitis, rhinitis, upper respiratory tract infections). The more frequent reporting of such infections in GH treated children is considered coincidental and/or attributable to underreporting in untreated children.

There is no evidence that the musculo-skeletal events were related to an acromegalic effect of treatment and a warning for scoliosis is reflected in the current SPC for growth hormones.

In general, changes in glucose, insulin, IGF-I, and HbA1c values were not clinically significant, however they were indicative of a compensatory response of the pancreas to the reduction in insulin sensitivity induced by growth hormone. As high IGF-I level were found in both treatment groups and as there is a lack of safety data on long-term high levels of IGF-I in children, a warning is introduced; if on repeated measurement, IGF-I levels exceed +2 SD, compared to references for age and pubertal status, the IGF-I / IGFBP-3 ratio could be taken into account to consider dose adjustment. At the moment the data are reassuring considering the effects on glucose metabolism, but the management of these patients should follow accepted clinical practice and include safety monitoring of fasting insulin and blood glucose prior to treatment and annually during treatment. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed and if overt diabetes occurs, growth hormone should not be administered. Long-term follow-up on safety is considered necessary.

Overall conclusion on benefit/risk

At its meeting of 18-19 March 2003, the CPMP considered the data presented by the MAHs and reached the following conclusion.

From the data on efficacy, it has been shown that Norditropin is effective for the treatment of growth disturbance (current height SDS <–2.5 and parental adjusted height SDS <–1) in short children born small for gestational age (SGA), with a birth weight and/or length below –2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later.

The short-term safety data related to the extended indication does not add any major unexpected risks and long-term safety data are necessary.

The MAHs committed to perform a post-marketing study to further investigate long-term metabolic effects after discontinuation of treatment in children born SGA.

On the basis of the efficacy data taking into account the concerns on long-term safety, the CPMP decided that the treatment should be initiated at a dose of 0.035 mg/kg/day and continued until final height is reached.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CPMP considered the referral made under article 7(5) of Commission Regulation EC No 541/95, for Norditropin and related invented names (see Annex I),
- the CPMP agreed that Norditropin is effective in the indication “Growth disturbance (current height SDS <–2.5 and parental adjusted height SDS <–1) in short children born small for gestational age (SGA), with a birth weight and/or length below –2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later”,

- no unexpected adverse events related to the extended indication were presented,
- the CPMP, as a consequence, considered the benefit/risk balance for the above-mentioned extension of indication to be favourable,

the CPMP has recommended the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Norditropin and related invented names (see Annex I).

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for Article 7(5) referral for Norditropin and related names.. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<*Invented name*>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<*To be completed as appropriate*>

Somatropin (recombinant DNA origin produced in E-coli)

1 mg of somatropin corresponds to 3 IU (International Unit) of somatropin

3. PHARMACEUTICAL FORM

<*To be completed as appropriate*>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children:
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

Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later.

Adults:
Pronounced growth hormone deficiency in known hypothalamic-pituitary disease (one other deficient axis, other than prolactin), demonstrated by two provocative tests after institution of adequate replacement therapy for any other deficient axis. Childhood onset growth hormone insufficiency, reconfirmed by two provocative tests.

In adults, the insulin tolerance test is the provocative test of choice. When the insulin tolerance test is contraindicated, alternative provocative tests must be used. The combined arginine-growth hormone releasing hormone is recommended. An arginine or glucagon test may also be considered; however these tests have less establish diagnostic value than the insulin tolerance test.

4.2 Posology and method of administration

The dosage is individual and must always be adjusted in accordance with the individual's response to therapy.

Prescription only.

<*Invented name*> should only be prescribed by doctors with special knowledge of the therapeutic indication of use.

Generally, daily subcutaneous administration in the evening is recommended. The injection site should be varied to prevent lipoatrophy.

Generally recommended dosages:

Children:
Growth hormone insufficiency
25-35 µg/kg/day or 0.7-1.0 mg/m^2/day
Equal to: 0.07-0.1 IU/kg/day (2-3 IU/m^2/day)

Turner syndrome
50 µg/kg/day or 1.4 mg/m^2/day
Equal to: 0.14 IU/kg/day (4.3 IU/m^2/day)

Chronic Renal Disease
50 µg/kg/day or 1.4 mg/m^2/day
Equal to: 0.14 IU/kg/day (4.3 IU/m^2/day)

Small for Gestational Age
35 µg/kg/day or 1 mg/m^2/day
Equal to: 0.1 IU/kg/day (3 IU/m^2/day)

A dose of 0.035 mg/kg/day is usually recommended until final height is reached. (See section 5.1).
Treatment should be discontinued after the first year of treatment, if the height velocity SDS is below +1.
Treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Adults:
Replacement therapy in adults
The dosage must be adjusted to the need of the individual patient. It is recommended to start treatment with a low dose 0.15-0.3 mg/day (equal to 0.45-0.9 IU/day). It is recommended to increase the dosage gradually at monthly intervals based on the clinical response and the patient's experience of adverse events. Serum insulin-like growth factor I (IGF-I) can be used as guidance for the dose titration.
Dose requirements decline with age. Maintenance dosages vary considerably from person to person, but seldom exceeds 1.0 mg/day (equal to 3 IU/day).

4.3 Contraindications

Any evidence of active malignant tumours.
Intracranial neoplasm must be inactive and anti-tumour therapy should be completed prior to institution of therapy.
Pregnancy and lactation. Please refer to Section 4.6.

Hypersensitivity to somatropin or to any of the excipients.

In the children with chronic renal disease treatment with <*Invented name*> should be discontinued at renal transplantation.

4.4 Special warnings and special precautions for use

Children treated with <*Invented name*> should be regularly assessed by a specialist in child growth. <*Invented name*> treatment should always be instigated by a physician with special knowledge of growth hormone insufficiency and its treatment. This is true also for the management of Turner syndrome, chronic renal disease and SGA. Data of final adult height following the use of <*Invented name*> are either not available (children with Turner syndrome) or limited (children with chronic renal disease).

The stimulation of skeletal growth in children can only be expected until the epiphysial discs are closed.

The dosage in children with chronic renal disease is individual and must be adjusted according to the individual response to therapy. The growth disturbance should be clearly established before <*Invented name*> treatment by following growth on optimal treatment for renal disease over one year. Conservative management of uraemia with customary medication and if needed dialysis should be maintained during <*Invented name*> therapy.

Patients with chronic renal disease normally experience a decline in renal function as part of the natural course of their illness. However, as a precautionary measure during <*Invented name*> treatment renal function should be monitored for an excessive decline, or increase in the glomerular filtration rate (which could imply hyperfiltration).

In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

In SGA children it is recommended to measure the IGF-I level before start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels exceed +2 SD compared to references for age and pubertal status, the IGF-I / IGFBP-3 ratio could be taken into account to consider dose adjustment.

Experience in initiating treatment in SGA patients near onset of puberty is limited. It is therefore not recommended to initiate treatment near onset of puberty.

Experience with patients with Silver-Russell syndrome is limited.

Some of the height gain obtained with treating short children born SGA with growth hormone may be lost if treatment is stopped before final height is reached.

Somatropin has been found to influence carbohydrate metabolism, therefore, patients should be observed for evidence of glucose intolerance.

Serum thyroxine levels may fall during treatment with <*Invented name*> due to the increased peripheral deiodination of T4 to T3.
In patients with a pituitary disease in progression, hypothyroidism may develop.
Patients with Turner syndrome have an increased risk of developing primary hypothyroidism associated with anti-thyroid antibodies.

As hypothyroidism interferes with the response to <*Invented name*> therapy patients should have their thyroid function tested regularly, and should receive replacement therapy with thyroid hormone when indicated.

In insulin treated patients adjustment of insulin dose may be needed after initiation of <*Invented name*> treatment.

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Leukaemia has been reported in a small number of growth hormone deficient patients some of whom have been treated with somatropin. Based on 10 years global assessment there is no increased risk of development of leukaemia during somatropin treatment. In patients in complete remission from tumours or malignant disease, growth hormone therapy has not been associated with an increased relapse rate. Nevertheless, patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of <*Invented name*> therapy.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders and Legg-Calvé-Perthes disease may occur more frequently in patients with short stature. These diseases may present as the development of a limp or complaints of hip or knee pain and physicians and parents should be alerted to this possibility.

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

In the event of severe or recurrent headache, visual problems, nausea, and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the growth hormone treatment should be discontinued.
At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Growth hormone deficiency in adults is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant glucocorticoid therapy may inhibit growth and thereby oppose the growth promoting effect of <*Invented name*>. The effect of growth hormone on final height can also be influenced by additional therapy with other hormones, e.g. gonadotrophin, anabolic steroids, estrogen and thyroid hormone.

4.6 Pregnancy and lactation

Currently there is insufficient evidence of safety of somatropin therapy during pregnancy. The possibility that somatropin is secreted in breast milk cannot be discounted.

4.7 Effects on ability to drive and use machines

No effects.

4.8 Undesirable effects

Fluid retention with peripheral oedema may occur and especially in adults carpal tunnel syndrome may be seen. The symptoms are usually transient and dose dependent, but may require dose reduction. Mild arthralgia, muscle pain, paresthesia may also occur in adults, but is usually self-limiting.

Adverse reactions in children are rare. The integrated <*Invented name*> database comprises data from children being treated for up to eight years. Headache has been reported with an incidence of 0.04 per patient year.

Formation of antibodies directed against somatropin has rarely been observed during <*Invented name*> therapy. The titres and binding capacities of these antibodies have been very low and have not interfered with the growth response to <*Invented name*> administration.

During treatment with <*Invented name*> local injection site reactions may occur.

Some rare cases of benign intracranial hypertension have been reported.

4.9 Overdose

Information on overdose and poisoning is lacking.
Acute overdosage can lead to low blood glucose levels initially, followed by high blood glucose levels. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycemia. Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: H 01 AC 01.
<*Invented name*> contains somatropin, which is human growth hormone produced by recombinant DNA-technology. It is an anabolic peptide of 191 amino acids stabilized by two disulphide bridges with a molecular weight of approximately 22.000 Daltons.

The major effects of <*Invented name*> are stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes.
When growth hormone deficiency is treated a normalization of body composition takes place resulting in an increase in lean body mass and a decrease in fat mass.
Somatropin exerts most of its actions through insulin-like growth factor I (IGF-I), which are produced in tissues throughout the body, but predominantly by the liver.
More than 90% of IGF-I is bound to binding proteins (IGFBP's) of which IGFBP-3 is the most important.

A lipolytic and protein sparing effect of the hormone becomes of particular importance during stress.

Somatropin also increases bone turnover indicated by an increase in plasma levels of biochemical bone markers. In adults bone mass is slightly decreased during the initial months of treatment due to more pronounced bone resorption, however, bone mass increases with prolonged treatment.

In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg/day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg/day) and +2.19 SDS (0.067 mg/kg/day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

5.2 Pharmacokinetic properties

I.v. infusion of <*Invented name*> (33 ng/kg/min for 3 hours) to nine growth hormone deficient patients, gave the following results: serum half-time of 21.1 ± 1.7 min., metabolic clearance rate of 2.33 ± 0.58 ml/kg/min. and a distribution space of 67.6 ± 14.6 ml/kg.

<*To be completed as appropriate*>

5.3 Preclinical safety data

<*To be completed as appropriate*>

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<*To be completed as appropriate*>

6.2 Incompatibilities

<*To be completed as appropriate*>

6.3 Shelf-life

<*To be completed as appropriate*>

6.4 Special precautions for storage

<To be completed as appropriate>

6.5 Nature and contents of container

<To be completed as appropriate>

6.6 Instructions for use and handling

<To be completed as appropriate>

7. MARKETING AUTHORISATION HOLDER

<To be completed as appropriate>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed as appropriate>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed as appropriate>

10. DATE OF REVISION OF THE TEXT

<To be completed as appropriate>