Unit: Technical Assessment Unit

Assessment report

(Norditropin Flexpro)

Administrative information:

Trade name of the medicinal product	Norditropin Flexpro
INN (or common name) of the active substance(s):	SOMATROPIN, RH-GH
Manufacturer of the finished product	Novo Nordisk A/S, Hallas Alle 1, DK-4400 Kalundborg, Denmark - DENMARK ;
Marketing Authorization holder	Novo Nordisk A/S, Novo Alle 1, DK-2880 Bagsvaerd, Denmark - DENMARK ;
Applied Indication(s):	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)
Pharmaceutical form(s) and strength(s):	Solution for injection. -10 mg/1.5 ml -15 mg/1.5 ml
Route of administration	S.C

List of abbreviations

B-hGH: Biosynthetic growth hormone.
CV: Cardiovascular.
CNS: Central Nervous System.
Cmax: Maximum plasma concentration.
DNA: Deoxyribonucleic acid.
EU: European Union.
FDA: Food Drug Administration.
GHD: growth hormone deficiency.
IGF-I: Insulin-like Growth Factor I.
IV: Intravenous.
LDL: low-density lipoprotein.
PK: Pharmacokinetic.
rh-GH: recombinant human growth hormone.
Ref-hGH: Reference human growth hormone.
SGA: Small for Gestational Age
SDS: Standard Deviation Score
SC: Subcutaneous.
Tmax: The time it takes for a drug to reach the maximum concentration (C_{max}).
WHO: World Health Organization.

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

- Norditropin® FlexPro® contains somatropin, which is human growth hormone (hGH) produced by recombinant DNA-technology.
- Specific activity/potency: 1 mg of anhydrous somatropin is equivalent to 3.0 IU of biological activity.
- Liquid Norditropin is a new formulation of the somatropin product Norditropin®.
- In order to launch a new disposable pen, the PDS290 pen-injector for Norditropin, Novo Nordisk is introducing a new cartridge, the Compact Cartridge to be used with the two different strengths: 10 mg and 15 mg per 1.5 mL corresponding to 6.7 mg/mL, and 10 mg/mL, respectively. The PDS290 pen-injector is developed based upon the current approved Norditropin NordiFlex prefilled pen.

2. **Quality aspects:**

2.2.1 Introduction

- As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **Manufacturer Of the active substance**:

- Novo Nordisk A/S, Hagedornsvej 1, 2820 Gentofte, Denmark - DENMARK ;

- **Specification**

- Specifications of hGH drug substance are well described in MA File and in accordance with (EU) pharmacopoeia edition 11.2 for somatropin and ICH Q6B
- Analytical procedures are well described.
- All methods are adequately validated
- The batch analysis results were compared, and all batches fulfilled the approved specifications.

- **Stability of drug substance**

Approved Shelf Life: 48 months

Approved Storage Conditions: Store at -20°C ± 5°C.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

Pharmaceutical Development including brief description on Components of drug product.

- The Detailed composition of Norditropin® SimpleXx® 10 mg and 15 mg Compact Cartridge are provided in MA files .
- Norditropin® SimpleXx® 10 mg uses a 1.5 mL Compact Cartridge, and has a colour-coded cap. And Norditropin® SimpleXx® 15 mg uses a 1.5 mL PDS290, and has a colour-coded cap.
- Different strengths of Norditropin® SimpleXx®: 10 mg and 15 mg per 1.5 mL

- corresponding to 6.7 mg/mL and 10 mg/mL, respectively.

Formulation Development

- A summary describing the development of the drug product is provided in MA file.
- The choice of the excipients , concentrations and their characteristics that can influence the drug product performance are discussed relative to their respective functions.
- Physicochemical and Biological Properties are provided in MA file.

Container closure system

- The components of the primary packaging for Norditropin® SimpleXx® are:
  1. 1.5 mL colorless glass cartridge meeting the Ph.Eur. type I criteria for glass containers.
  2. Laminated rubber disc meeting the Ph.Eur. Type I criteria for rubber closures for aqueous preparations for parenteral use (the Bromo butyl face of the disc is facing the product).
  3. Rubber plunger meeting the Ph.Eur. type I criteria for rubber closures for aqueous preparations for parenteral use.

Microbiological Attributes.

- A Certain concentration of phenol was chosen as antimicrobial preservative.

Compatibility.

- The compatibility between Norditropin® SimpleXx® 10 mg and 15 mg and primary packaging has been investigated and the analytical results show that the drug product is compatible with the rubber materials as no stability indicating parameters were altered as a result of the increased contact area.

- **Manufacture of the drug product:**

Description of manufacturing process and process controls along with manufacturers and responsibilities.

- The Finished Product is manufactured at Novo Nordisk A/S, Hallas Alle 1, DK-4400 Kalundborg, Denmark;
- Full description of drug product manufacturing process is provided in MA file.
-The manufacturing process of liquid Norditropin®, process parameters are controlled within defined limits to ensure control of the process and secure that the drug product meets specifications.

Control of critical steps and intermediates

- Critical steps are well defined along with justification for Controls of each Critical parameterin MA file.

- **Process validation and / or evaluation.**

- Validation Summary summarise the process validation (PV) activities performed for the manufacturing process of liquid Norditropin®.
- All the manufacturing steps and procedures in the manufacturing have been validated.
- The results showed that the manufacturing process is consistent using three consecutive batches.
- Validation data is provided in MA file.

- **Product specification:**

- Specifications and acceptance criteria of Norditropin® FlexPro® 10 mg/1.5 ml and Norditropin® FlexPro® 15 mg/1.5 ml are in accordance with (Somatropin injection) monograph Eur.ph.
- The specification limits and analytical methods for Norditropin® SimpleXx® are justified based on ICH Q6B guidelines, Ph. Eur. Monographs and batch analysis.
- All excipients used are compendial and listed in this section supported by their pharmacopeial monographs.
- All excipients are of non-animal derived origin and tested according to monographs in Ph. Eur., USP/NF and JP, no novel excipient is used.

- **Reference Standards or Materials.**

- Somatropin (hGH) Secondary Reference Material (SRM) is used, and calibrated against the current WHO International Standard for Somatropin.

- **Container closure system.**

- A description of container closure system composition and compatibility with the drug product are discussed in MA file.
- The container closure system for Norditropin® SimpleXx® comprises the compact cartridge (primary packaging) and the PDS290 pen-injector for Norditropin® SimpleXx® (secondarypackaging).

- **Stability of the drug product.**

Approved Shelf Life: 24 months
Approved Storage Conditions:
Store in a refrigerator (2°C - 8°C) in the outer carton, in order to protect it from light

- Do not freeze
- Do not store close to any cooling elements.
- Don't shake

After first opening: Store for a maximum of 4 weeks in a refrigerator (2°C -8°C).
Alternatively, the medicinal product may be stored for a maximum of 3 weeks below 25°C.

- Don't freeze

3. Non –clinical aspect:

- **Norditropin FlexPro®** contains somatropin, which is a human growth hormone produced by recombinant DNA-technology. The major effects of somatropin are stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes. On Mar 03, 2010, that the FDA has approved Norditropin FlexPro®, a pre-filled injection pen to be used by children and adults with growth hormone disorder.

  - For Norditropin® FlexPro®, the nonclinical (Module 4) documentation submitted in Egypt are the same as those previously submitted and approved in the European Union (EU). As there are no changes to the active substance, formulation composition, route of administration, dosing regimen, or overall clinical exposure and the only difference relates to the delivery device no additional nonclinical studies are considered necessary.

  - **Poloxamer 188:** a surfactant added to stabilize the formulation. As poloxamer 188 has limited human SC data, a limited safety program including toxicity studies, effect on reproduction, genotoxic potential, and absorption and excretion have been performed in mice, rats, rabbits and dogs.

- **Pharmacology:** The biological activity (**weight gain assay, receptor binding assay**) has been found to be similar for an accelerated degraded Liquid Norditropin preparation, all major degradation products, somatropin control and in-house standard somatropin calibrated against a WHO standard. However, in the weight gain assay 3 of the minor degradation products, dimer and polymers of somatropin and des-phepro-1,2 somatropin showed decreased biological activity. This is not likely to influence the potency of Liquid Norditropin as degraded Liquid Norditropin contains less dimer and polymers compared to degraded Norditropin®. An increased biological activity in the weight gain assay was observed for isoasp-107 somatropin as well as for the somatropin control probably caused by heavy stress of the protein molecules during isolation and purification. Based upon these biological tests, the adequate activity of Liquid Norditropin after storage has been demonstrated and the efficacy of Liquid Norditropin and Norditropin® should be similar. In experiments that have explored the principal functional body systems, Liquid Norditropin and degraded Liquid Norditropin had no effects at all on the CV and respiratory systems in rats. The only CNS effect observed in the Irwin Observation test in mice was a temporary slight reduction in spontaneous activity during the first 30 min. after dosing of Liquid Norditropin 8mg/kg. The minor anti-diuretic effect with concomitant effect on urinary electrolyte excretion of Liquid Norditropin and degraded Liquid Norditropin in rats were comparable to those produced by the same doses of Norditropin® and are well known for somatropin. Liquid Norditropin, degraded Liquid Norditropin, major degradation products and Norditropin® behaved identically in all studies indicating that the vehicle for Liquid Norditropin and the degradation products do not alter **the safety pharmacology** profile from that of Norditropin®.

- **Pharmacokinetics:** The plasma concentration of somatropin increased rapidly following SC administration and C_{max} was observed at 30-45 min after injection (T_{max}). A comparison amongst studies with different doses did not show dose dependency in T_{max}. After a single SC administration, the half-life of somatropin varied between 48 and 79 min. The half-life after SC administration is longer compared with IV administration (8-44 min) reflecting the absorption from subcutis. No Metabolism, Excretion or PK Drug Interactions studies have been performed due to the endogenous nature of the

drug. In general, no differences were observed between Norditropin® and Liquid Norditropin, Liquid Norditropin and degraded Liquid Norditropin, or any of the degradation products (desamido-l49, desamido-152, isoasp-l30, and cyclic imide-l30 somatropin) and Ref-hGH. The PK parameters were comparable amongst studies. Thus, the PK of somatropin did not depend on the formulation or storage of Liquid Norditropin.

- A range of studies in laboratory species using SC administration indicates that **poloxamer 188** is rapidly eliminated from plasma with a half-life of 0.5-2 h and is excreted unchanged in urine within a few hours of administration (certainly within 24 h). Only trace quantities are found in tissues. Data on accumulation after repeated SC dosing are weak, being based on single doses of [^{14}C]-Poloxamer 188 administered during the study.

- **Toxicology:** Single and repeated dose toxicity and local tolerance studies did not reveal any toxic effect of the degraded product or damage to muscle tissue of Liquid Norditropin. Studies with Norditropin® did not provide evidence of mutagenic potential and Liquid Norditropin is just a formulation of Norditropin®. Also, it is concluded that B-hGH did not cause adverse effects on pregnancy of rats which could indicate a potential teratogenic effect. Additionally, B-hGH did not cause adverse effects on pregnancy pre-and post-natal performance or offspring development in the rat. The immunogenicity tests in mice transgenic for gene of the human somatropin, its major degradation products, product related impurities and of a degraded Liquid Norditropin preparation showed that no antibody response could be induced indicating that no immunological response can be expected against authentic human somatropin.

- Animal toxicity studies on **poloxamer 188** indicate little significant effect after a single dose. Repeated dose studies by the SC route indicated only two effects of relevance. At SC doses of 100 mg/kg and above, poloxamer 188 caused vacuolation of the renal tubular cells and a reduction in incidence of basophilic foci in the kidney in rats without evidence of cell damage and the change was reversible. In dogs there was slight reaction at the injection site associated with administration of poloxamer 188 following repeated administration, but changing the injection site routinely should eliminate the problem, if it occurs. Other differences, when compared with controls, occurred in clinical chemical assays at high doses in the rat studies, but effects were slight, inconsistent and of uncertain reproducibility. They should not be regarded as being of consequence to the administration of low doses to man (no more than 2.25 mg). Administration of high doses of poloxamer 188 by SC injection in a conventional series of reproductive studies did not indicate any effects on reproduction or on fetuses in rats or rabbits. Genotoxicity studies indicated no mutagenic or clastogenic effects.

- **Overall conclusion:** There is no indication in the toxicology studies presented, nor in the safety pharmacology screen, of any unexpected effects that might be ascribed to non-hGH components of the preparation. It may be concluded that, as far as may be ascertained by tests conducted in laboratory animals, the Nordisk Gentofte preparation of B-hGH is as safe and effective as Pituitary human GH.

4. Clinical aspect:

➢ Clinical Overview

Norditropin® (somatropin) is a recombinant human growth hormone (rhGH) that replaces or supplements endogenous growth hormone in children and adults with growth hormone deficiency (GHD) and selected growth disorders. Somatropin binds to growth hormone receptors on target cells, triggering intracellular signaling pathways that stimulate growth, metabolism, and tissue development. Many of its effects are mediated through insulin-like growth factor-I (IGF-I), produced primarily in the liver and locally in target tissues.

Norditropin has been extensively studied across pediatric and adult populations, with long-term clinical experience supporting its established efficacy and safety profile in approved indications.

➢ Clinical Efficacy and Immunogenicity

Pediatric Populations

Noonan Syndrome

Treatment with Norditropin resulted in clinically meaningful improvements in height velocity and final adult height. Height gains of approximately 1.5-1.6 SDS were observed, corresponding to an average increase of 9-11 cm at adulthood. Younger age at treatment initiation was associated with greater height gain, and no relevant gender differences were identified.

Turner Syndrome

Across randomized, long-term studies, Norditropin significantly improved final height, with dose-dependent benefits. Up to 70% of treated patients achieved final heights within the normal range. Dose escalation regimens produced greater gains in height SDS and sustained increases in height velocity during early treatment years.

Children Born Small for Gestational Age (SGA)

In both long-term and short-term studies, Norditropin demonstrated dose-dependent increases in height velocity and height SDS. A substantial proportion of treated children reached normal adult height, with the higher dose (0.067 mg/kg/day) providing greater and more sustained growth responses.

Adult Growth Hormone Deficiency

In adults with childhood-onset or adult-onset GHD, Norditropin significantly improved body composition by:

- Increasing lean body mass
- Reducing total and abdominal fat mass
- Improving lipid parameters (including LDL cholesterol)
- Increasing markers of bone formation
- These benefits were sustained during long-term follow-up.

Immunogenicity

As with all protein therapeutics, somatropin may induce antibody formation. Anti-GH antibodies were detected in a minority of pediatric patients; however, these antibodies were generally non-neutralizing and **did not affect growth response, efficacy, or safety**. Clinically relevant neutralizing antibodies were rare, and no meaningful impact on treatment outcomes was observed.

- **Clinical Safety**

Pediatric Safety

Across indications (Noonan syndrome, Turner syndrome, and SGA), Norditropin was generally well tolerated. The most frequently reported adverse events were common childhood infections (e.g., upper respiratory tract infections, otitis media, gastroenteritis).

Key safety observations include:

No evidence of treatment-induced cardiac hypertrophy in Noonan syndrome

Dose-related increases in otitis media in Turner syndrome

Transient glucose intolerance observed more frequently at higher doses, without confirmed cases of persistent diabetes mellitus

No acceleration of bone maturation or consistent worsening of scoliosis

IGF-I levels increased appropriately and generally remained within the reference range

Adult Safety

In adults, the most common adverse reactions included peripheral edema, arthralgia, myalgia, and paresthesia, consistent with the known fluid-retention effects of growth hormone. These events were typically mild to moderate and transient. A small increase in glucose intolerance and type 2 diabetes mellitus was observed in early trials using higher-than-currently-recommended doses.

Post-Marketing Experience

Post marketing data confirm the established safety profile. Rare cases of serious hypersensitivity reactions (including anaphylaxis), pancreatitis, and new-onset diabetes mellitus have been reported. Reports of leukemia in GH-treated children remain inconclusive, with no definitive causal relationship established.

- **Benefit–Risk Analysis**

Norditropin provides well-documented and clinically meaningful benefits in growth outcomes for children with growth disorders and metabolic and body composition improvements in adults with GHD. These benefits are supported by long-term clinical trials and extensive real-world experience.

The identified risks are well characterized, generally dose-dependent, and manageable through:

Appropriate patient selection

Individualized dose titration

Routine monitoring of growth, IGF-I levels, glucose metabolism, and clinical symptoms

When used according to approved prescribing information, the benefits of Norditropin clearly outweigh its potential risks.

- **Overall Conclusion**

Norditropin® FlexPro® represents an extension of the well-established Norditropin product line, with identical formulation, comparable exposure, and no new safety concerns. Extensive clinical evidence demonstrates sustained efficacy in improving growth and metabolic outcomes across approved pediatric and adult indications, with a predictable and manageable safety profile.

Based on the totality of clinical, pharmacological, and post-marketing data, the **benefit-risk profile of Norditropin® FlexPro® is favorable and equivalent to the already registered Norditropin NordiFlex®**, supporting its use in the proposed indications in children and adults with growth hormone deficiency and related growth disorders.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved