SUMMARY BASIS OF DECISION (SBD)

PrOMNITROPE™

Somatropin
5.8 mg /vial, powder for solution
5 mg/1.5 mL and 10 mg/1.5 mL, solution

Sandoz Canada Inc.
Submission Control Number: 113380

Date Issued | 2009/09/14

Health Products and Food Branch
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Health Canada

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- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), POMNITROPEMD, Somatropine, 5,8 mg/flacon, 5 mg/1,5 mL, 10 mg/1,5 mL, Poudre pour solution, Sandoz Canada Inc., Numéro de contrôle de la présentation : 113380
FOREWORD

Health Canada’s Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within the evaluation reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the ‘Reader’s Guide to the Summary Basis of Decision - Drugs’ to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled ‘How Drugs are Reviewed in Canada’. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the ‘Summary Basis of Decision Initiative - Frequently Asked Questions’ document. These documents are all available on the Health Canada Web site.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Health Canada Web site.

For further information on a particular product, readers may also access Web sites of other regulatory jurisdictions, available under ‘Related Links’ on the Health Canada Web site. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada Web site for other drug policies and guidance documents. In particular, readers may wish to refer to the ‘Management of Drug Submissions Guidance’.
TABLE OF CONTENTS

1 PRODUCT AND SUBMISSION INFORMATION ............................................................... 1

2 NOTICE OF DECISION ......................................................................................................... 2

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION.............................................. 3

   3.1 Quality Basis for Decision ................................................................................................ 5
       3.1.1 Drug Substance (Medicinal Ingredient) ............................................................... 5
       3.1.2 Drug Product ........................................................................................................ 6
       3.1.3 Facilities and Equipment ..................................................................................... 9
       3.1.4 Adventitious Agents Safety Evaluation ................................................................. 9
       3.1.5 Conclusion ............................................................................................................ 9

   3.2 Non-clinical Basis for Decision ...................................................................................... 10
       3.2.1 Pharmacodynamics ............................................................................................ 10
       3.2.2 Pharmacokinetics ............................................................................................... 10
       3.2.3 Toxicology .......................................................................................................... 10
       3.2.4 Conclusion .......................................................................................................... 12

   3.3 Clinical Basis for Decision.............................................................................................. 12
       3.3.1 Comparative Pharmacokinetic and Pharmacodynamic Studies........................ 12
       3.3.2 Clinical Efficacy ................................................................................................. 13
       3.3.3 Clinical Safety ...................................................................................................... 15
       3.3.4 Authorized formulations/strengths of Omnitrope ............................................... 16

   3.4 Benefit/Risk Assessment and Recommendation............................................................. 16
       3.4.1 Benefit/Risk Assessment ..................................................................................... 16
       3.4.2 Recommendation ............................................................................................... 17

4 SUBMISSION MILESTONES .............................................................................................. 18
1 PRODUCT AND SUBMISSION INFORMATION

Brand Name: PrOMNITROPE™
Manufacturer/Sponsor: Sandoz Canada Inc.
Medicinal Ingredient: Somatropin
International Non-proprietary Name: Somatropin
Strengths: 5.8 mg/vial, 5 mg/1.5 mL, 10 mg/1.5 mL
Dosage forms: Powder for solution, solution
Route of Administration: Subcutaneous (SC)
Drug Identification Numbers (DINs): Multiple DINs:
02325055 - 5.8 mg/vial powder for solution
02325063 - 5 mg/1.5 mL solution
02325071 - 10 mg/1.5 mL solution
Therapeutic Classification: Human Growth Hormone
Non-medicinal Ingredients: Vial contains: glycine, disodium hydrogen phosphate heptahydrate, and sodium dihydrogen phosphate dihydrate. Solvent: benzyl alcohol, water for injection. 5.0 mg/1.5 mL cartridge contains: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, mannitol, poloxamer 188, benzyl alcohol, and water for injection. 10.0 mg/1.5 mL cartridge contains: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, glycine, poloxamer 188, phenol, and water for injection.
Submission Type and Control Number: New Drug Submission, Control Number: 113380
Date of Submission: 2007/04/03
Date of Authorization: 2009/04/20
2 NOTICE OF DECISION

On April 20, 2009, Health Canada issued a Notice of Compliance to Sandoz Canada Inc. for the drug product Omnitrope.

Omnitrope contains the medicinal ingredient somatropin which is a recombinant human growth hormone.

Omnitrope is indicated for:

- **Growth Hormone Deficiency (GHD) in Children:** Long-term treatment of children with growth failure due to an inadequate secretion of endogenous growth hormone. Other causes of short stature should be excluded.
- **Adult Growth Hormone Deficiency (GHD):** Long-term replacement therapy in adults with growth hormone deficiency due to underlying hypothalamic or pituitary disease or who were growth deficient during childhood. Growth hormone deficiency should be confirmed by an appropriate growth hormone stimulation test. Patients who were diagnosed as growth hormone deficient during childhood must be retested before treatment starts.

The safety and efficacy of Omnitrope in geriatric (≥65 years of age) and pediatric (<3 years of age) patients have not been evaluated in clinical studies.

Treatment with somatropin stimulates linear growth and normalizes concentrations of Insulin-like Growth Factor-I (IGF-I) in children with GHD. In adults with GHD, treatment with somatropin results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.

The market authorization was based on quality, non-clinical, and clinical information submitted.

Based on the similarity principles for the subsequent entry biologics, a reduced clinical package was accepted. It consists of one repeated-dose toxicity study and six comparative pharmacodynamic (PD) studies in rats (in two of these, Omnitrope was compared with Genotropin®), two local tolerance studies in rabbits, one bioavailability study and four comparative pharmacokinetic (PK)/PD studies in healthy adults, and five Phase III clinical efficacy and safety studies in GHD children. The PK/PD data were comparable between Omnitrope and Genotropin®, and bioequivalence was demonstrated among the different formulations and strengths of Omnitrope. In the treatment of children with GHD, Omnitrope had a clinical efficacy and safety profile that was comparable to the reference product Genotropin®.
The studies also demonstrated that the lyophilized powder and liquid formulations of Omnitrope had comparable clinical efficacy and safety profiles.

Although, there were no clinical studies conducted with Omnitrope in adult GHD patients, Health Canada agreed that the use of Omnitrope in adult GHD patients is supported in consideration of the similar product quality characteristics of Omnitrope and Genotropin® and the similar pathophysiology of adult GHD to GHD in children. In addition, comparative non-clinical, human PK/PD, and clinical efficacy and safety studies in children were conducted to demonstrate comparable clinical profiles between Omnitrope and Genotropin®.

Omnitrope (somatropin) is presented in two dosage forms: a powder for solution (5.8 mg/vial), and solution (5 mg/1.5 mL and 10 mg/1.5 mL). The dosage and administration schedule of Omnitrope should be individualized for each patient. The doses should be given by subcutaneous injections (administered preferably in the evening). Dosing guidelines are available in the Product Monograph.

Omnitrope is contraindicated for patients that show evidence of neoplastic activity, for pediatric patients with closed epiphyses, and for patients with acute critical illness following cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure. Omnitrope is also contraindicated in patients with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment.

Omnitrope lyophilized powder when reconstituted with the diluent Bacteriostatic Water for Injection (benzyl alcohol preserved) and Omnitrope 5.0 mg/1.5 mL solution which also contains the preservative benzyl alcohol, should not be administered in newborns or in patients with a known sensitivity to benzyl alcohol. Omnitrope is contraindicated in patients who are hypersensitive to somatropin or to any ingredient in the formulations. Omnitrope should be administered under the conditions stated in the Product Monograph taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Omnitrope are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Omnitrope is favourable for the indications stated above.

**3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION**

On April 13, 2007, Health Canada received a New Drug Submission (NDS) for Omnitrope from Sandoz Canada Inc. The NDS (with a reduced clinical package) was filed as a Subsequent Entry Biologic (SEB) submission, as the sponsor claimed
comparability between Omnitrope and Genotropin® [an innovator drug that was issued a Notice of Compliance (NOC) on January 19, 1998, for marketing in Canada but was never marketed in Canada]. Genotropin® was authorized for the following two indications:

- For the long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone. Other causes of short stature should be excluded.
- Long-term replacement therapy in adults with growth hormone deficiency (GHD) due to underlying hypothalamic or pituitary disease or who were growth deficient during childhood.

Due to a number of deficiencies in the NDS for Omnitrope, a Notice of Deficiency (NOD) for Omnitrope was issued on March 19, 2008. Additional information was required to assess the efficacy of Omnitrope in the treatment of GHD in children, and to assess the proper use of Omnitrope for Canadian populations. The NOD response was received on June 10, 2008. Within the NOD response, the sponsor responded to all of the deficiency comments. The extrapolation of the indication for treatment of GHD from the paediatric population to the adult population was justified on the basis that Omnitrope and Genotropin® had similar quality characteristics, comparable non-clinical and clinical profiles supported by data, and a written clinical/scientific rationale by the sponsor. A Canadian Risk Management Plan (RMP) was agreed upon, and on April 20, 2009 an NOC was issued for Omnitrope with the same indications as Genotropin®.

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Omnitrope is favourable in the treatment of the indications stated above. The NDS complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the NOC pursuant to section C.08.004 of the Food and Drug Regulations.

SEBs are not "generic biologics" and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply. Authorization of an SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug.
3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

Somatropin, the medicinal ingredient of Omnitrope, is a human growth hormone manufactured by recombinant deoxyribonucleic acid (DNA) technology. The amino acid sequence is identical to that of the human growth hormone of pituitary origin (somatropin). The Omnitrope NDS was filed as an SEB drug. The known elements required for a new drug were evaluated, as well as the data provided to demonstrate that Omnitrope (the powder for solution and the liquid formulations) is comparable to the reference product, Genotropin®. This second level of evaluation was required so that a recommendation to Health Canada’s clinical review staff could be made regarding the acceptability of the provision of a reduced clinical package in the NDS.

Manufacturing Process and Process Controls

The drug substance, somatropin, is a recombinant human growth hormone produced in Escherichia Coli. The manufacturing process is divided into three parts: fermentation, isolation, and purification. The drug substance is then filtered and filled into bottles and stored frozen.

The manufacturing process is considered to be adequately controlled within justified limits. In-process controls performed during manufacture were reviewed and are considered acceptable. The materials used in the manufacture are considered to be suitable and meet the standards appropriate for their intended use.

Characterization

Characterization studies have demonstrated that the somatropin molecule for Omnitrope exhibits the expected primary, secondary and tertiary structures. The studies also demonstrated that this recombinant human growth hormone is comparable to the somatropin hormone from Genotropin®. Detailed characterization studies were performed to provide assurance that the medicinal ingredient consistently exhibits the desired characteristic structure and biological activity.
Similar profiles and levels of product-related impurities/substances were obtained with Sandoz somatropin when compared to Genotropin®. Appropriate tests are adequately controlling the levels of product- and process-related impurities.

**Control of Drug Substance**

The drug substance specifications and analytical methods used for the quality control of somatropin are considered acceptable. Validation reports were provided and are considered satisfactory for all analytical procedures used for release and stability testing of somatropin.

Batch analysis results were reviewed and all results comply with the specifications and demonstrate consistent quality of the batches produced.

The proposed packaging components are considered acceptable.

**Stability**

Stability study results obtained from long-term, accelerated, and stress testing show that Sandoz somatropin is a stable compound when packaged as proposed over the proposed storage period and storage conditions.

**3.1.2 Drug Product**

**Description and Composition**

Omnitrope is supplied in the following dosage forms and strengths for injection:

- Solution: 5 mg/1.5 mL cartridge
- Solution: 10 mg/1.5 mL cartridge
- Powder for solution: 5.8 mg/vial

The Omnitrope solutions are clear, colourless, sterile solutions packaged in a colourless glass cartridge closed on one side with a plunger and on the other side with a stopper sealed with an aluminium disc. The two different strengths, 5 mg/1.5 mL and 10 mg/1.5 mL, are intended for use with the Pen 5 and Pen 10 devices, respectively, both of which are licensed by Health Canada. Each strength is supplied in pack sizes of one cartridge per carton, five cartridges per carton, and ten cartridges per carton.
The two strengths of Omnitrope solutions have different compositions:

- The Omnitrope 5 mg/1.5 mL cartridge contains: 5.0 mg of somatropin, 1.3 mg disodium hydrogen phosphate heptahydrate, 1.6 mg sodium dihydrogen phosphate dihydrate, 3.0 mg poloxamer 188, 13.5 mg benzyl alcohol, 52.5 mg mannitol and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH.

- The Omnitrope 10 mg/1.5 mL cartridge contains: 10.0 mg of somatropin, 1.70 mg disodium hydrogen phosphate heptahydrate, 1.35 mg sodium dihydrogen phosphate dihydrate, 3.0 mg poloxamer 188, 4.5 mg phenol, 27.75 mg glycine and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH.

The Omnitrope powder for solution, 5.8 mg/vial, is a sterile, white or almost white, lyophilized powder packaged in a 2 mL clear, glass vial, stoppered with a bromobutyl rubber stopper and sealed with an aluminium flip-off cap. Each vial contains 5.8 mg somatropin, 27.6 mg glycine, 2.09 mg disodium hydrogen phosphate heptahydrate, and 0.56 mg sodium dihydrogen phosphate dihydrate. Each vial is supplied with a diluent cartridge of Bacteriostatic Water for Injection which contains 1.5% benzyl alcohol as a preservative. The reconstituted drug product is intended for use with the Omnitrope Pen L device, also licensed by Health Canada. Each carton contains 8 vials of Omnitrope powder for solution and 8 cartridges of diluent.

All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations. The compatibility of Sandoz somatropin with the excipients is demonstrated by the stability data presented on the proposed commercial formulations.

**Pharmaceutical Development**

Changes to the manufacturing process and formulation made throughout the pharmaceutical development are considered acceptable upon review. Several studies which justified the type and proposed concentration of preservative/excipient to be used in the drug product were reviewed and are considered to be acceptable.
**Manufacturing Process and Process Controls**

All manufacturing equipment, in-process manufacturing steps, and detailed operating parameters were adequately described in the submitted documentation and are found to be acceptable. The manufacturing process is considered to be adequately controlled within justified limits.

The validation process is considered to be complete. Validation reports were submitted for in-process and release testing of the drug product, and no anomalies were present. The results for all of the batches were within the proposed specification limits.

**Control of Drug Product**

The test specifications are considered acceptable to control the drug product, and the impurity limits were set according to International Conference on Harmonisation (ICH) recommendations.

Through Health Canada’s lot release testing and evaluation program, consecutively manufactured final product lots were tested, evaluated, and found to meet the specifications of the drug product and demonstrate consistency in manufacturing.

The analytical methods used for release and stability testing of the Omnitrope drug products are appropriate and have been successfully validated. The container closure systems met all validation test acceptance criteria.

**Stability**

For the Omnitrope solutions, the long-term stability data support shelf-lives of 24 months at 5 ±3°C for Omnitrope 5 mg/1.5 mL and 18 months at 5 ±3°C for Omnitrope 10 mg/1.5 mL.

For the Omnitrope powder for solution, the long-term stability data support a shelf-life of 36 months at 5 ±3°C. The long-term stability data for the Benzyl Alcohol diluent support a shelf-life of 36 months at either 5 ±3°C or 25 ±2°C/60% Relative Humidity.
3.1.3  Facilities and Equipment

The facilities involved in the manufacture of the drug substance, somatropin, and the two Omnitrope solutions were inspected by a qualified team of inspectors from the Biologics and Genetic Therapies Directorate, Health Canada. The on-site evaluation (OSE) and the review of the responses to the Exit Notice observations were found to be satisfactory.

An OSE of the facility involved in the manufacture of the Omnitrope powder for solution was not warranted since the facility was recently approved by Health Canada for another product produced by the company within the last three years.

3.1.4  Adventitious Agents Safety Evaluation

Materials of animal origin are not used in the manufacture of the Sandoz somatropin drug substance. Raw materials of bovine origin are sourced from countries that are either considered as bovine spongiform encephalopathy (BSE) -free (Australia, New Zealand) or as low risk [United Stated of America (USA)]. Whereas bovine milk was used as a raw material, it was confirmed that this material was derived from animals fit for human consumption. Materials of porcine origin are sourced from Canada or from the USA.

3.1.5  Conclusion

The Chemistry and Manufacturing information submitted for Omnitrope has demonstrated that the drug substance and drug products can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes.

Omnitrope in its liquid and lyophilized forms was found to be similar to Genotropin® (lyophilized powder) with regards to the identity of the somatropin protein, the potency determined by the cell proliferation assay and the physico-chemical purity. Generally, Omnitrope and Genotropin® have similar impurity profiles. The sum of impurities in Genotropin® and in both formulations of Omnitrope was comparable but slight differences exist in the quantities of individual impurities between the products. Submission of a reduced clinical package is acceptable based on the comparability data presented for Omnitrope drug substance and drug products to the reference product, Genotropin®.
3.2 Non-clinical Basis for Decision

3.2.1 Pharmacodynamics

Pharmacodynamic (PD) studies utilizing the rat weight-gain bioassay demonstrated that various batches of Omnitrope, including lots manufactured at both pilot and commercial scales, bulk substances and finished Omnitrope products, elicited the specific PD action of body-weight gain. In addition, all products were comparable in potency to international reference standards of human somatropin and were therefore within the specifications of the United States Pharmacopoeia 1998.

The rat tibial width assay was used to compare the potency of Omnitrope, Norditropin®, and Genotropin® formulations with low and high contents of product-related impurities, to the international reference standard somatropin. It was demonstrated that all products increased the width of the proximal epiphysis of the tibia in immature hypophysectomized rats, and the potency of all of these products were comparable and in accordance with the European Pharmacopeia 1987 - Method A.

The potencies calculated in the rat weight-gain assays and in the rat tibial width assay could not be compared directly due to procedural differences. However, since these assays utilized the same international standard, the potencies were considered comparable.

3.2.2 Pharmacokinetics

Non-clinical pharmacokinetic (PK) studies to study absorption, distribution, metabolism, excretion, and drug interactions were not conducted. It was considered reasonable not to have conducted these studies because of our knowledge of Omnitrope and other somatropins, the information already available about their behaviour in various animal species, and the fact that it is a heterologous protein which is likely to stimulate an immune response in foreign species.

3.2.3 Toxicology

Single-Dose Toxicity

No single-dose toxicity study was performed with the Omnitrope drug substance.
**Repeat-Dose Toxicity**

A repeat-dose study was conducted in rats at dose levels of 0 (vehicle control, sodium chloride), 2 or 8 mg/kg body weight (bw)/day, for 14 consecutive days. The high dose provided an ~160-fold safety margin above the maximum human dose level. All dose levels were well-tolerated and were not associated with any signs of treatment-related toxicity. The primary findings were observed for females only and included a dose-related increase in body weight, and increased food consumption in the 8 mg/kg bw group. These findings were indicative of a metabolic effect of Omnitrope, and were considered to reflect its specific PD action.

**Genotoxicity**

Genotoxicity studies were not performed with the Omnitrope drug substance. As Omnitrope is a recombinant protein of known structure, and as its formulation contains only simple ingredients, there is no reason to expect that it would exhibit any genotoxic activity. For that reason and in accordance with the suggestions of the ICH Guideline S6 (Preclinical Testing of Biotechnology-derived Pharmaceuticals), it was decided that such testing was not required.

**Carcinogenicity**

Carcinogenicity studies were not performed with the Omnitrope drug substance. The absence of these experiments is consistent with the nature of the preparation and the recommendations of the ICH Guideline S6 (Preclinical Testing of Biotechnology-derived Pharmaceuticals).

**Reproductive and Developmental Toxicity**

Animal reproductive and developmental toxicity studies were not conducted with Omnitrope. It is not known whether Omnitrope can cause foetal harm when administered to a pregnant woman or if it can affect reproductive capability.

**Local Tolerance**

Local tolerance studies in rabbits demonstrated that there were no marked differences between the reactions at the administration site induced by Omnitrope powder for solution, Omnitrope solution, and Genotropin® and their respective vehicle. Furthermore, even an increased level of product-related substances did not have an impact on its local tolerance. Daily subcutaneous (SC) administration did elicit haematoma formation, with
the incidence and severity increasing with time. However, hematomas rapidly disappeared after the last administration, with complete resolution for all animals by Day 11. Histopathological changes included acute or subacute inflammation sometimes associated with minor haemorrhage, and mononuclear cell infiltration, particularly fibrohistiocytic cells associated with fibrosis. Therefore, it is recommended that the SC injection site be rotated on a daily basis.

3.2.4 Conclusion

The pharmacology and toxicology studies for this drug submission are considered acceptable. Non-clinical toxicity testing demonstrated that Omnitrope was well-tolerated in rats. However, dose-related gross and histopathological changes were noted at the SC injection sites, and so it is recommended that the injection site be rotated on a daily basis. In addition, reproduction studies have not been conducted, and so special consideration should be given prior to administration to pregnant women. In conclusion, the non-clinical toxicology data base was considered adequate to assess the safety profile of Omnitrope and support its use in humans, provided the appropriate safety precautions are taken, as described above.

3.3 Clinical Basis for Decision

3.3.1 Comparative Pharmacokinetic and Pharmacodynamic Studies

Four comparative Phase I studies compared PK/PD characteristics among the various formulations/strengths of Omnitrope and between Omnitrope and Genotropin®, all administered at a single dose of 5 mg via SC route, in cross-over design trials, in healthy adults.

- Study EP2K-99-PhlUSA, a 2-arm cross-over trial comparing Omnitrope powder for solution (5.8 mg/vial) versus Genotropin® powder for solution.
- Study EP2K-00-PhIAQ, a 2-arm cross-over trial comparing Omnitrope powder for solution (5.8 mg/vial) versus Omnitrope solution (5 mg/1.5 mL).
- Study EP00-104, a 3-arm cross-over trial comparing Omnitrope powder for solution (5.8 mg/vial), Omnitrope solution (5 mg/1.5 mL) and Genotropin® powder for solution.
- Study EP00-105, a 3-arm cross-over arm trial comparing Omnitrope powder for solution (5.8 mg/vial), Omnitrope solution (10 mg/1.5 mL) and Genotropin® powder for solution.
Bioequivalence was demonstrated among the different formulations and strengths of Omnitrope products. Bioavailability of Omnitrope powder for solution (5.8 mg/vial), Omnitrope solution 5 mg/1.5 mL, and Omnitrope solution 10 mg/1.5mL was comparable to that of Genotropin® 5.8 mg (5 mg/mL) at the same dose administered via the same route in adult healthy volunteers.

The study results for the following PD parameters: Insulin-like Growth Factor 1 (IGF-1), Insulin-like Growth Factor Binding Protein 3 (IGFBP-3), and Nonesterified Fatty Acids (NEFA) were highly comparable after single doses of 5 mg of the different strengths and formulations of Omnitrope and Genotropin®.

### 3.3.2 Clinical Efficacy

Five Phase III clinical efficacy and safety studies were conducted in children with GHD.

- Three sequential, randomized, open-label, parallel studies (EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIIIAQ) were performed in the same cohort of 89 GHD children with Omnitrope powder for solution (5.8 mg/vial), Omnitrope solution (5 mg/1.5 mL) and the reference product Genotropin® 5 mg/mL powder. Forty-four patients received Omnitrope powder for solution (5.8 mg/vial) and 45 patients received Genotropin® for 9 months. In both groups, somatropin was administered as a daily SC injection at a dose of 0.03 mg/kg. Subsequently, after 9 months of treatment, patients who had received Genotropin® switched to Omnitrope solution (5.0 mg/1.5 mL). The Omnitrope powder for solution was continued beyond 9 months with the same dose. After 15 months of treatment, all patients were switched to Omnitrope solution (5.0 mg/1.5 mL) to collect long-term efficacy and safety data for Omnitrope solution. The route of administration and dose was the same for Omnitrope powder for solution and Omnitrope solution.

- Study EP2K-00-PhIIib-E was a single-arm study to confirm long-term safety and efficacy of Omnitrope liquid formulation. The study was performed with Omnitrope solution (5 mg/1.5 mL), administered daily via SC injection at a dose of 0.03 mg/kg, in 50 GHD children. Interim analyses were conducted at 12, 24, and 30 months of growth hormone (GH) treatment.

- Study EP2K-02-PhIII-Lyo was a single-arm study to confirm long-term safety and efficacy of Omnitrope lyophilized formulation. The study was performed with Omnitrope powder for solution (5.8 mg/vial), administered daily via SC injection at a dose of 0.03 mg/kg in 51 GHD children. Interim analyses were conducted at 12 and 24 months of GH treatment.
The three sequential studies and Study EP2K-02-PhIII-Lyo were conducted in clinical centres in Poland and Hungary, while Study EP2K-00-PhIIIb-E was conducted in Spain.

Key efficacy end-points included height velocity (HV), height velocity standard deviation score (HVSDS), and height standardised for age and sex standard deviation score (HSDS); and serum levels of IGF-1 and IGFBP-3.

On March 19, 2008, an NOD was issued as additional information was required to assess the efficacy and proper use of Omnitrope in the treatment of GHD in children from the Canadian population. Issues related to use of the national standards and the Tanner standard for growth assessment, the cross-over of treatments in the sequential trials, and the short duration of comparison of Omnitrope with Genotropin® were identified.

In response to the NOD, the sponsor provided a re-analysis of the efficacy data. The difference of the efficacy parameters calculated using the national standards versus using the Center for Disease Control of the United States in 2000 (the CDC standard) was discussed. In spite of the minor differences on the key efficacy parameters observed from the calculations using the different standards, the efficacy conclusion remained very similar. The sponsor compared the efficacy of all drugs and/or formulations across all studies based on the results of the re-analysis, and the results indicated that there were only minor differences on the efficacy parameters. Using a longitudinal modelling method, the sponsor compared efficacy between Omnitrope and Genotropin® after 9 months treatment from the sequential trials (studies EP2K-99-PhIII, EP2K-00-PhIIIFo) and the data for the same treatment duration of other studies (Studies EP2K-00-PhIIIb-E and EP2K-02-PhIII-Lyo). No major differences were observed, and no apparent treatment-by-centre interactions were reported.

In summary, the three sequential Phase III studies EP2K-99-PhIII, EP2K-00-PhIIIFo, and EP2K-00-PhIIIb-A demonstrated that Omnitrope had a clinical efficacy and safety profile in the treatment of GHD children which was comparable to Genotropin®, and that the Omnitrope powder for solution (5.8 mg/vial) and Omnitrope solution (5.0 mg/mL) had comparable clinical efficacy and safety profiles in the treatment of children with GHD. In the other two studies (EP2K-02-PhIII-Lyo and EP2K-00-PhIIIb-E), the efficacy results for lyophilized Omnitrope (5.8 mg/vial) and Omnitrope solution (5 mg/mL) were consistent with the results obtained in the previous studies.

Although no pivotal Phase III clinical studies were conducted with Omnitrope in GHD adults, Health Canada agreed that it was acceptable to extrapolate the GHD indication of Omnitrope from the paediatric population to the adult population, after the assessment of the written rationale provided by the sponsor. Acceptance of justification for the
extrapolation was based on the principles outlined in the draft SEB guidance document. The use of Omnitrope in adult GHD patients was supported in consideration of the similar product quality characteristics of Omnitrope and Genotropin® and the similar pathophysiology of adult GHD to GHD in children and in adults. In addition, comparative non-clinical, human PK/PD, and clinical efficacy and safety studies in children were conducted to demonstrate comparable clinical profiles between Omnitrope and the reference product. The indication for adult GHD was carefully worded to include only two adult sub-populations (a) GHD in adults due to underlying hypothalamic or pituitary disease; and (b) GHD in adults who were growth hormone deficient during childhood. It is also required that GHD in adults should be confirmed by an appropriate growth hormone stimulation test and that patients who were diagnosed as growth hormone deficient during childhood must be retested before treatment starts.

### 3.3.3 Clinical Safety

The clinical safety of Omnitrope was primarily based on the five Phase III studies described previously. See section 3.3.2 Clinical Efficacy.

The AEs observed in the clinical studies conducted with Omnitrope (powder for solution and solution) were generally of the type expected for Genotropin® and other GH products. The long-term safety data of Omnitrope also showed a comparable safety profile to that published for Genotropin® or for other GH treatments.

The most frequent AEs (>5%) with Omnitrope powder for solution in the paediatric population were injection site reaction (12%), eosinophilia (9%) and headache (6%). The most frequent AEs with Omnitrope solution were increased glycosylated hemoglobin A1c (9%), eosinophilia (7%) and injection site reaction (7%).

Adverse drug reactions that most commonly resulted in clinical intervention with Omnitrope powder for solution in the paediatric population were hypothyroidism (3%) and headache (2%). Adverse drug reactions that most commonly resulted in clinical intervention with Omnitrope solution in the paediatric population were headache (4%) and upper respiratory tract infections (2%).

Two serious AEs (1%) on worsening of a pre-existing scoliosis were reported in the clinical trials with Omnitrope in the paediatric population.
In the three sequential pivotal studies, the safety comparison between Omnitrope and Genotropin® was limited to only 9 months of treatment due to the treatment switch from Genotropin® to Omnitrope after completion of Study EP2K-99-PhIII. During these 9 months, the safety profiles were comparable. Based on the data presented, there was no increase of treatment-related adverse events (AEs) after switching the test products.

Preparations of Omnitrope contain a small amount of host cell *Escherichia coli* peptides (HCP). Anti-HCP antibodies are found in a small number of patients treated with Omnitrope, but these appear to be of no clinical significance.

### 3.3.4 Authorized formulations/strengths of Omnitrope

The authorized dosage form of Genotropin® in Canada is the powder for solution at three strengths: 1.5 mg, 5.8 mg, and 13.8 mg each supplied in a pre-assembled Intra-Mix reconstitution device. The final concentrations after reconstitution are 1.3 mg/mL, 5 mg/mL and 12 mg/mL, respectively.

Based on the draft SEB guidance, the dosage form, strength, and route of administration of SEBs should be within those granted to the reference product. However, Omnitrope solution 5 mg/1.5 mL was used in the pivotal trial as a part of integrated sequential clinical trials and in the single-arm safety and efficacy study conducted to evaluate its long-term efficacy and safety. Authorization of this formulation/strength was based on the integrated data from all of these studies.

Comparative PK/PD data was provided to compare the PK/PD characteristics of Omnitrope solution 10 mg/1.5 mL with either Omnitrope powder for solution (5.8 mg/vial) or Genotropin® powder for solution. The PK and PD parameters obtained from all three drugs were comparable. Hence, the Omnitrope solution 10 mg/1.5 mL was authorized for marketing.

### 3.4 Benefit/Risk Assessment and Recommendation

#### 3.4.1 Benefit/Risk Assessment

Based on the results of the clinical trials, it has been demonstrated that Omnitrope has comparable efficacy to the reference product, Genotropin®, in terms of clinical parameters (height, HSDS, HV, and HVSDS). In addition, results from two single-arm long-term efficacy and safety studies confirmed that the efficacy profiles of the powder for solution (5.8 mg/vial) and solution (5 mg/1.5 mL) were comparable. It was
demonstrated that Omnitrope improves growth acceleration in paediatric patients suffering from GHD. The use of Omnitrope in adult GHD patients is supported in consideration of the similar product quality characteristics of Omnitrope and Genotropin®, the similar pathophysiology of adult GHD to GHD in children, and the comparable clinical profiles between Omnitrope and Genotropin®.

The most frequent drug-related AEs were eosinophilia, headache, injection site hematoma, injection site haemorrhage, injection site inflammation and contusion, hypothyroidism, increased glycosylated haemoglobin, pain in an extremity, and scoliosis. The majority of drug-related AEs were mild or moderate in intensity. The safety profile of Omnitrope is similar to that of Genotropin.

The sponsor provided an RMP which was assessed by Health Canada and is considered acceptable.

Overall, the studies demonstrated that Omnitrope was well-tolerated and associated with a manageable safety profile. Based on the safety and efficacy profile, the benefits of Omnitrope therapy seem to outweigh the risks. Restrictions to manage risks associated with the identified safety concerns have been incorporated into the Omnitrope Product Monograph.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Omnitrope is favourable in the treatment of the indications stated above. The NDS complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the NOC pursuant to section C.08.004 of the Food and Drug Regulations.

SEBs are not "generic biologics" and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply. Authorization of an SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug.
## 4 SUBMISSION MILESTONES

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