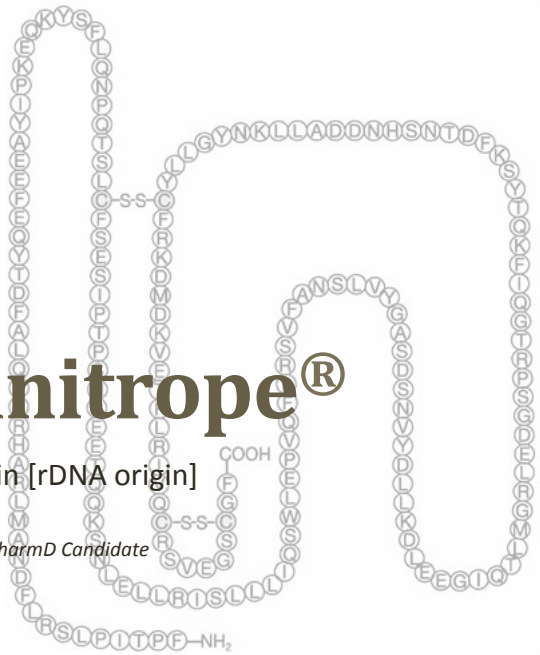

Omnitrope®

Somatropin [rDNA origin]

Sarah Myers, PharmD Candidate

Background

Human Growth Hormone (GH) & GH Disorders

Human Growth Hormone

- Human Growth Hormone (GH) is an endogenous protein critical for normal growth and development
- Product of the anterior pituitary
- Released in pulse-like fashion, bursts occurring overnight
- Triggers growth and development of tissues throughout the entire body

Human Growth Hormone

- **Physiologic effects**
  - Decreases glucose utilization by peripheral tissues
    - Impairs tissue glucose uptake
    - Decreases insulin-receptor sensitivity
  - Increases lipolysis
  - Increases muscle mass
  - Stimulates gluconeogenesis in hepatocytes

Human Growth Hormone

- The growth-promoting effects are predominately mediated by **insulin-like growth factors (IGFs)** or *somatomedins*
  - GH stimulates IGF-1 formation in liver
- IGF directly stimulates cell proliferation & growth
  - **IGF-1: primarily regulates growth after birth**
  - IGF-2: primarily regulates growth in utero
- Binds to Insulin-like growth factor 1 receptor (IGF1R)
  - Present on many cells throughout the body
  - Tyrosine kinase receptor→ initiating pathway of intracellular signaling

Growth Hormone Excess

- Excessive production of growth hormone
  - Acromegaly
  - Gigantism
- Rare: affecting up to 70 per 1 million adults
  - GH-secreting pituitary adenoma is most common cause
- Mainstay of treatment: surgical removal of adenoma
- Pharmacologic treatment includes:
  - GH receptor antagonists (**Pegvisomant**)
  - Dopamine agonists (**bromocriptine** and **cabergoline**)
  - Somatostatin analogs (**Octreotide**)

Growth Hormone Deficiency

- Inadequate production of growth hormone is referred to as a growth-related disorder
- Growth-related disorders may be present at birth or may develop with time
- *Short stature*: height greater than 2 standard deviations below the mean AND lower than the 3rd percentile for a specific age group
  - Prevalence: > 1.8 million children in the US

Growth Hormone Deficiency

- Growth hormone deficient short stature is congenital
  - GHRH deficiency, GH gene deletion, pituitary aplasia, etc.
- Growth hormone insufficiency is acquired
  - Pituitary or hypothalamic tumors, cranial irradiation, trauma, CNS infections, etc.
  - Pharmacologic agents may induce transient insufficiency:
    - Glucocorticoids
    - Methylphenidate (and other CNS stimulants)
    - LH-releasing hormone agonists

Growth Hormone Deficiency

Growth Hormone Deficient Short Stature

- **Mainstay of Treatment:**
  - Recombinant growth hormone
- Ten recombinant GH options are currently marketed in the US
  - Genotropin, Humatrope, Norditropin, Nutropin, **Omnitrope**, Saizen, Serostim, Tev-Tropin, Zomacton, Zorbtive
- Goals of therapy
  - Improve poor growth velocity in children
  - Maximize patient height outcome
  - Increase bone mass, muscle mass
  - Decrease fat mass

Omnitrope®

Medication Overview

Classification & Indication:

- **Pharmacologic Category:** Growth Hormone
- **FDA Approved Indications:**
  - **Pediatric:**
    - Growth failure secondary to growth hormone deficiency (GHD)*
    - Prader-Willi Syndrome
    - Small for Gestational Age
    - Turner Syndrome
    - Idiopathic Short Stature
  - **Adult:**
    - Growth hormone deficiency
      - Adult onset
      - Childhood onset

Classification & Indication:

- **Off-label Uses**
  - HIV-associated adipose redistribution syndrome (HARS)
  - HIV-associated wasting or cachexia
  - Short-bowel Syndrome
  - Cognitive improvement associated with TBI

Mechanism of Action

- **Mechanisms of Action:**
  - Omnitrope binds to the GH receptor in cell membrane
  - Facilitates growth of linear bone, skeletal muscle, and organs through chondrocyte proliferation and differentiation, lipolysis, protein synthesis, and hepatic gluconeogenesis via stimulation of IGF secretion
  - Facilitates erythropoietin stimulation
  - Increases trans-mucosal transport of water, electrolytes, and nutrients across the GI tract

Dosage Forms

- Omnitrope® cartridge
  - 5 mg/ 1.5 mL for Omnitrope® Pen 5
    - AWP: $640 per pen
  - 10 mg/ 1.5 mL for Omnitrope® Pen 10
    - AWP: $1280 per pen
- Omnitrope 5.8 mg/vial
  - Requires reconstitution of somatropin powder and diluent
- *Studies suggest that Omnitrope injection pen offers an easy and convenient device that can contribute to better adherence*
  - Facilitates self-injection
  - No reconstitution required
  - Minimizes pain

Administration

- Subcutaneous injection
  - Pediatric GHD
    - Weight-based dosing (mg/kg/week)
    - Divided into daily doses
    - Recommended dosing for CHD short stature: 0.3 mg/kg/wk
  - Adult GHD
    - Maximum 0.08 mg/kg/week divided into daily injections
  - Rotate injection sites
    - Thigh
    - Buttocks
    - Abdomen
  - Cartridges disposed of after 28 days from first use

Administration

- **Step-wise Instructions for use**
  - Load cartridge into pen
  - Attach needle
  - Prime the pen at 0.1mg dose
  - Dial dose
  - Inject
  - Remove needle
  - Store

Contraindications

- Severe obesity with Prader-Willi Syndrome
- Diabetic retinopathy
- Closed epiphyses
- Acute critical illnesses
- Malignancies

Precautions

- History of neoplasm
- Impaired glucose tolerance/ DM
- Intracranial hypertension
- Fluid retention
- Hypothyroidism
- Hypopituitarism
- Upper respiratory obstruction/ Sleep Apnea
- Scoliosis

Monitoring

- Alkaline phosphatase
- Parathyroid hormone (PTH)
- IGF-I
- Serum glucose
- Electrolytes
- Growth/development parameters

Adverse Reactions

Table 1. Incidence of Adverse Reactions Reported in ≥ 5% Pediatric Patients with GHD During Treatment with Omnitrope® Cartridge (N=86)

Adverse Event	n (%)
Elevated HbA1c	12 (14%)
Eosinophilia	10 (12%)
Hematoma	8 (9%)

N=number of patients receiving treatment
n=number of patients who reported the event during study period
%=percentage of patients who reported the event during study period

Adverse Reactions

Table 2. Incidence of Adverse Reactions Reported in ≥ 5% Pediatric Patients with GHD During Treatment with Omnitrope® for Injection (N=44)

Adverse Event	n (%)
Hypothyroidism	7 (16%)
Eosinophilia	5 (11%)
Elevated HbA1c	4 (9%)
Hematoma	4 (9%)
Headache	3 (7%)
Hypertriglyceridemia	2 (5%)
Leg Pain	2 (5%)

N=number of patients receiving treatment
n=number of patients who reported the event during study period
%= percentage of patients who reported the event during study period

Drug Interactions

- Glucocorticoids
  - Inhibit growth-promoting effects of GH
- CYP450 cleared medications
- Insulin & oral hypoglycemic agents
  - Omnitrope may decrease effectiveness of anti-diabetic agents
- Oral estrogens
  - May decrease effects of Omnitrope

Table 4. Contents of Omnitrope® Cartridges and Vial

Product	Cartridge 5 mg/ 1.5 mL	Cartridge 10 mg/ 1.5 mL	For Injection 5.8 mg/ vial
Component			
Somatropin	5 mg	10 mg	5.8 mg
Disodium hydrogen phosphate heptahydrate	1.3 mg	1.70 mg	2.09 mg
Sodium dihydrogen phosphate dihydrate	1.6 mg	1.35 mg	0.56 mg
Poloxamer 188	3.0 mg	3.0 mg	-
Mannitol	52.5 mg	-	-
Glycine	-	27.75 mg	27.6 mg
Benzyl alcohol	13.5 mg	-	-
Phenol	-	4.50 mg	-
Water for Injection	to make 1.5 mL	to make 1.5 mL	-
Diluent (vials only)			**Bacteriostatic Water for Injection**
Water for injection			to make 1.14 mL
Benzyl alcohol			17 mg

Efficacy

Table 5. Baseline Growth Characteristics and Effect of Omnitrope® after 9 and 15 Months of Treatment

Treatment Duration	Treatment Group	Treatment Group
0 - 9 months	**Omnitrope® for Injection** (n=44)	**Another Somatropin Product** (n=45)
9 - 15 months	**Omnitrope® for Injection** (n=42)	**Omnitrope® Cartridge** (n=44)
Treatment Parameter	**Mean (SD)**	**Mean (SD)**
Height velocity (cm/yr)		
Pre-treatment	3.8 (1.2)	4.0 (0.8)
Month 9	10.7 (2.6)	10.7 (2.9)
Month 15	8.5 (1.8)	8.6 (2.0)
Height velocity SDS		
Pre-treatment	-2.4 (1.3)	-2.3 (1.1)
Month 9	6.1 (3.7)	5.4 (3.2)
Month 15	3.4 (2.6)	3.2 (2.9)
Height SDS		
Pre-treatment	-3.0 (0.7)	-3.1 (0.9)
Month 9	-2.3 (0.7)	-2.5 (0.7)
Month 15	-2.0 (0.7)	-2.2 (0.7)
IGF-1*		
Pre-treatment	159 (92)	158 (43)
Month 9	291 (174)	302 (183)
Month 15	300 (225)	323 (189)
IGFBP-3*		
Pre-treatment	3.5 (1.3)	3.5 (1.0)
Month 9	4.6 (3.0)	4.0 (1.5)
Month 15	4.6 (1.3)	4.9 (1.4)

Lopez-Siguero J, Perez M, Balser S, Khan-Boluki J. **Long-term Safety and Efficacy of the Recombinant Human Growth Hormone Omnitrope (R) in the Treatment of Spanish Growth Hormone Deficient Children: Results of a Phase III Study.** *Advances In Therapy* [serial online]. n.d.;28(10): 879-893.

CLINICAL EFFICACY & SAFETY

Lopez-Siguero J, et. al.

- Multi-center, phase III clinical trial
- **Population:** Pre-pubertal GHD children (n=70), ages 4-12 yo
- **Treatment:** 0.03 mg/kg/day Omnitrope subcutaneously
- Measured changes every 3-6 months in:
  - height
  - height standard deviation score(HSDS)
  - height velocity (HV)
  - HV standard deviation score (HVSDS)
  - serum insulin-like growth factor (IGF)-1
  - insulin-like growth factor binding protein (IGFBP)-3 levels
- 69 of the 70 participants completed the 2 year study duration
  - *Major non-adherence was reason for withdrawal of participant*

Lopez-Siguero J, et. al.

- Mean exposure to medication was 3.7±1.0 years
- Results
  - Significant increase in mean body height
    - 9.4 cm over 1 year
    - 31.1 cm over 4 years
  - HSDS
  - HV values
    - Baseline value of 3.86 +/- 1.25 cm/yr
    - Peak mean of 11.1 +/- 4.0 cm/yr at month 3
  - Mean IGF-1 serum levels
    - Increased by 123.2 ng/mL at year 1
    - Increased by 275.0 ng/mL at year 4
  - Mean IGFBP-3 serum levels

Lopez-Siguero J, et. al.

- **Safety**
  - 426 total adverse events in 55 of 70 patients (79%)
    - 94% mild intensity
  - 17 drug-related adverse events in 10 of 70 patients
    - AE per patient year treated was 0.066
      - Edema, swelling, arthralgia, injection site reactions
- Study conclusion: *At a dose of 0.03 mg/kg/day, Omnitrope was safe, effective, and well tolerated during long-term treatment of children with GHD.*

Lopez-Siguero J, et. al.

- **Strength**
  - Up to 5 year study period
- **Limitations of study**
  - No comparative/control group
  - No randomization
  - Multicenter; Spain-only
  - Few patients followed full 5 years (n=5)

Bioequivalence

- Omnitrope is a bioequivalent recombinant growth hormone
  - Compared to Genotropin (Pfizer) in phase I and III trials
  - Demonstrates clinical comparability
- Two randomized, double-blind, three-way crossover studies were carried out in 36 participants
  - Pharmacokinetic parameters were similar for the three treatments
  - Area under the concentration–time curve (AUC) and C_{max} aligned with bioequivalence standards
  - Pharmacodynamic parameters for IGF1 were similar
  - No differences in adverse events were observed
- **Study Conclusion:** Omnitrope 3.3 mg/ml solution, 6.7 mg/ml solution, and 5 mg/ml powder, and Genotropin 5 mg/ml powder are bioequivalent, demonstrate similar PK and PD profiles, and are equally safe.
  - Considered therapeutically interchangeable

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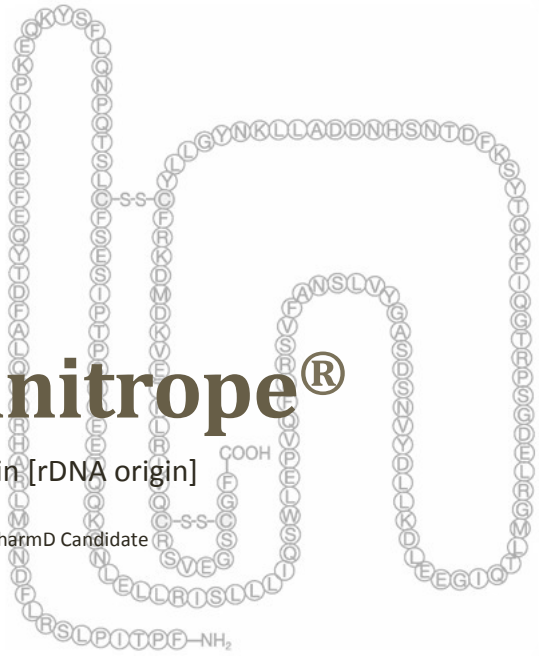

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