DBC Drug Review Summary

Questions for consideration:

1. Is there sufficient evidence that Humatrope® (somatropin) provides a therapeutic advantage, in terms of mortality, morbidity or quality of life over other biosynthetic human growth hormone products or compared with placebo, in the treatment of adults with adult-onset or childhood-onset growth hormone deficiency for the Drug Benefit Council (the Council) to recommend that the Ministry of Health Services (the Ministry) list Humatrope® on the PharmaCare formulary for this indication?

Issues for consideration:

- Currently, four forms of somatropin, (Humatrope®, Nutropin®, Nutropin AQ® and Saizen®) are PharmaCare Limited Coverage benefits for children 20 years of age and under, when prescribed by an endocrinologist at the British Columbia Children's Hospital for true growth hormone deficiency or chronic renal insufficiency.
- On February 8, 2010, the Council reviewed somatropin (Omnitrope®) for the approved Health Canada indications and recommended Omnitrope® be listed similar to other growth hormones which are listed as Limited Coverage drugs with criteria as stated above. The complete Omnitrope DBC Recommendation and Reasons for Recommendation is available on the memory stick.

Generic/brand name:

somatropin/Humatrope®

Dosage forms/strengths:

- vial of 5 mg (approximately 15 IU) somatropin for injection; and
- Cartridges of 6 mg (approximately 18 IU), 12 mg (approximately 36 IU), or 24 mg (approximately 72 IU) somatropin for injection.

Manufacturer:

Eli Lilly Canada Inc.

Health Canada approved indications:

Pediatric Patients:

1. Growth Hormone Deficiency:

Humatrope (somatropin for injection) is indicated for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and whose epiphyses are not closed.

2. **Turner Syndrome:**

Humatrope is indicated for the treatment of short stature associated with Turner Syndrome in patients whose epiphyses are not closed.

3. **Patients with Idiopathic Short Stature (ISS)**:

Humatrope is indicated for the long-term treatment of idiopathic short stature defined by:

- Normal birth weight;
- Careful diagnostic evaluation that excludes other known causes of short stature that should be either observed or treated by other means;
- Height at least 2.25 standard deviation scores (SDS) below the mean for age and sex; and
- Height velocity below the 25th percentile for bone age and sex over 12 months of observation and unlikely to permit attainment of adult height in the expected range.

Humatrope treatment for idiopathic short stature should be prescribed only for those patients whose epiphyses are not closed and should be managed by physicians who have sufficient knowledge of idiopathic short stature and the efficacy/safety profile of Humatrope.

Patients with Short stature Homeobox-containing gene (SHOX) deficiency:
Humatrope is indicated for the treatment of short stature or growth failure in children with *SHOX* (short stature homeobox-containing gene) deficiency whose epiphyses are not closed.

Adult Patients:
Humatrope is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiencies, who meet either of the following two criteria:

1. **Adult Onset:** Patients must have somatotropin deficiency syndrome, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; **or**

2. **Childhood Onset**: Patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Confirmation of the diagnosis of adult growth hormone deficiency in both groups by appropriate growth hormone stimulation test is usually required. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

Indication requested:

The manufacturer is requesting a recommendation of reimbursement by the BC Fair PharmaCare program for the indication of the replacement for endogenous growth hormone in adults with growth hormone deficiency. (See above for the complete indication.)

Patent expiry dates:

There are two patents remaining for Humatrope, expiring January 25, 2011 and August 2, 2011.

Disease state overview:

The estimated prevalence of GHD in the adult population is 2 per 10,000 (about half from childhood-onset, half from adult-onset, mainly pituitary tumours). The incidence of pituitary tumours is approximately 1 per 100,000 per year. GH is synthesized and released from the anterior pituitary gland and is under control of GH releasing hormone (GHRH) which stimulates GH secretion, and somatostatin which inhibits GH secretion.

For more information see the UBC Faculty of Medicine's March 2010 report, pages 8-9.

Current coverage status and cost comparison of comparators (based on costs from CDR):

Drug/ Comparator	**Strength**	**PharmaCare Status**	**Cost/Unit**	**Dose Range** *(from CPS)*	**Annual Cost of Therapy*** Adult patients 70kg
somatropin (Humatrope®)	5.0 mg/vial Lyo powder 6, 12 & 24 mg per cartridge Lyo powder, cartridge and diluent syringe	Limited Coverage and Under review	$49.94 / mg	Initiate: not more than 0.006 mg/kg/day Maximum: 0.0125 mg/kg/day	$8,000-$16,000
somatropin (Omnitrope™)	5 mg/1.5 ml 10 mg/1.5 ml	Under Review	$33.34 /mg	Starting: 0.15-0.3 mg/day. Maximum maintenance: 1.33 mg daily	$2,000-$16,000
somatropin (Nutropin® and Nutropin AQ®)	5.0 & 10.0 mg/vial Lyo powder 10 mg/2 ml vial 10 mg/2 ml cartridge	Limited Coverage	$41.67 /mg	Starting: 0.006 mg/kg Maximum: 0.025 mg/kg Over 35 years: 0.0125 mg/kg	$6,000-$27,000 $13,000
somatropin (Saizen®)	3.3 mg/vial & 5 mg/vial Lyo powder	Limited Coverage	$46.55 /mg	Starting: 0.005 mg/kg/day After 4 weeks: 0.01 mg/kg/day	$6,000-$12,000

*Rounded to the nearest thousand dollars

Key outcome measures:

For a list of the outcome measures used in the reviewed clinical trials see the UBC Faculty of Medicine's March 2010 report, pages 14-15.

Known Unapproved or Potential Indications for Use:

Human growth hormone is used:

- as an anti-aging agent
- to improve athletic performance, and
- for bodybuilding purposes.

It is also used in combination with other performance enhancing drugs, such as anabolic steroids.

Adverse Drug Reaction Reporting from Health Canada as of September 30, 2009:

During the period January 1, 1985 – September 30, 2009, there were a total of 11 reports of adverse events involving human growth hormone in patients more than 20 years old. Seven of these reports were for serious adverse events, including two deaths and one not recovered/not resolved.

Health Canada Issues:

The November 14, 2003 issue of the Canadian Adverse Reaction Newsletter warned against the use of Human Growth Hormone in children with Prader-Willi syndrome.

Miscellaneous Issues:

No issues found.

Provincial Summary:		
Date Completed:	**March 30, 2010**	
Province	**Status**	**Details**
British Columbia	UR	
Alberta	LWC	
Manitoba	NB	
New Brunswick	NB	
Newfoundland & Labrador		
Nova Scotia		
Ontario		
Prince Edward Island		
Quebec	LWC	SOMATROPIN: 1. for treatment of growth hormone deficiency in persons whose bone growth has terminated and who meet the following criteria: • somatropin serum or plasma level between 0 and 3 g/mL in a pharmacological test; In persons who have a multiple hypophyseal hormone deficiency, and to confirm a deficiency acquired during childhood or adolescence, only one pharmacological stimulation test is necessary. In the case of an isolated growth hormone deficiency, two tests are required. The insulin hypoglycemia test is recommended. If this test is contraindicated, the arginine test alone, or combined with the GHRH, may be substituted for it. Where the arginine test is combined with the GHRH, the value must be 9 g/L; • in the case of adult onset, the deficiency must be secondary to hypophyseal or hypothalamic disease, surgery, radiotherapy or trauma;
Yukon		
Saskatchewan		

LST – Listed as a full benefit in the formulary; **LWC** – A restricted benefit for which coverage criteria are published (e.g., exception drug status, limited use benefit, special authorization with published criteria); **LSM** – list in similar manner as other drugs in class or group; **NLT** – Reviewed by drug plan and decision is not to list; **UR** – Under review; **CBC** – Not listed as a benefit but covered on a case-by-case basis – e.g., Section 8 (individual clinical review) in Ontario or Special authorization in MB; **EXC** – Excluded (belongs to category of drugs that the drug plan excludes on basis of policy or mandate – e.g., fertility agents); **APA** – Covered by another program or agency (e.g., Cancer Boards, HIV/AIDS program); **NS** – No Submission received.

Financial Implications:

The Ministry of Health Services Budget Impact Analysis (BIA), which includes BC PharmaCare Drug Expenditure data and BC Utilization data, is available on memory stick.

Somatropin (Humatrope®) Budget Impact Analysis – March 17th, 2010

Therapy: Somatropin for injection (Humatrope®)
- 5mg Vial
- 6mg Cartridge
- 12mg Cartridge
- 24mg Cartridge

Objective of this Report:

The objective of this report is to evaluate the budget impact to PharmaCare of listing somatropin (Humatrope®) as a Limited Coverage drug for the treatment of growth hormone deficiency in adults above the age of 20 years.

Drug Information Background:

- Somatropin (Humatrope®) for subcutaneous injection is indicated in adults for long-term treatment of growth hormone deficiency due to an inadequate secretion of endogenous growth hormone (GH) in adults provided they meet the following criteria:
  - **Adult Onset:** Patients must have somatropin deficiency syndrome, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma.
    or
  - **Childhood Onset:** Patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

- Currently PharmaCare does not reimburse any drugs for the treatment of growth hormone deficiency in adults.

- PharmaCare currently reimburses other somatropin products based on the following Limited Coverage criteria:
  - For children 20 years of age and under, when prescribed by an endocrinologist at the British Columbia Children's Hospital for true growth hormone deficiency or chronic renal insufficiency.

Ray Ghouse
Contact: Ray.Ghouse@gov.bc.ca

Table 1 lists the cost information of Humatrope® and comparator treatments considered in this BIA.

Table 1: Cost Information for Humatrope® and Comparator Treatments

Drug Name	Strength and Dosage Form	PharmaCare Status	Cost/Unit	Dose range	Annual Cost of Therapy*
Somatropin (Humatrope®)	5mg/ vial Lyo powder 6mg, 12mg, 24mg per cartridge Lyo powder, cartridge and diluents syringe	Limited Coverage/Under Review	$49.94/mg	Initiate at not more than 0.006mg/kg/day Maximum: 0.0125 mg/kg/day	$8,000-$16,000
Somatropin (Omnitrope®)	5mg/1.5ml cartridge 10mg/1.5ml cartridge	Under Review	$33.34/mg	Starting dose is 0.15-0.3mg/day maximum maintenance dose 1.33 mg daily	$2,000-$16,000
Somatropin (Nutropin®, and Nutropin AQ®)	5 & 10 mg/vial Lyo powder 10mg/ 2ml vial 10mg/2ml cartridge	Limited Coverage	$41.67/mg	Starting 0.0006 mg/kg Maximum 0.025 mg/kg over 35 years 0.0125 mg/kg	$6,000-$27,000 $13,000
Somatropin (Saizen®)	3.33mg vial, 5mg vial Lyo powder	Limited Coverage	$46.55/mg	Start 0.005mg/kg/day After 4 weeks to 0.01 mg/kg/day	$6,000 - $12,000
Somatropin (Genotropin®)	1.5mg vial 5.8mg vial 13.8mg vial	Non Benefit			-
Somatropin (Serostim®)	5mg vial 6mg vial	Non Benefit			-

*Note: All costs include 7% pharmacy markup.*Annual costs rounded to the nearest $1,000 for adult patients weighing 70kg.*

Table 2a shows the BC and PharmaCare utilization of somatropin treatments for all patients and Table 2b for adult patients above the age of 20 years over a one-year period.

Table 2a: BC and PharmaCare Utilization for all GH Patients, 01/12/2008-30/11/2009

Chemical	BC # of Patients	# of Patients registered for PC	# of Patients with PC Coverage	Average Cost Per Patient Day of Therapy	BC Total Cost Claimed	Total PharmaCare Paid
Humatrope® (somatropin) Omnitrope® (somatropin) Nutropin® (somatropin) Saizen® (somatropin) Genotropin® (somatropin) Serostim® (somatropin)	S22					
Total (Distinct Patients)	**564**	**368**	**211**	**$41.76**	**$4,751,671**	**$2,602,038**

Note: All costs include pharmacy markup and dispensing fees.

Table 2b: BC and PharmaCare Utilization for Adult GH Patients, 01/12/2008-30/11/2009

Chemical	BC # of Patients	# of Patients registered for PC	# of Patients with PC Coverage	Average Cost Per Patient Day of Therapy	BC Total Cost Claimed	Total PharmaCare Paid
Humatrope® (somatropin) Omnitrope® (somatropin) Nutropin® (somatropin) Saizen® (somatropin) Genotropin® (somatropin) Serostim® (somatropin)	S22					
Total (Distinct Patients)	**277**	**118**	S22	**$29.24**	**$1,186,281**	S22

Note: All costs include pharmacy markup and dispensing fees.

Budget Impact Analysis:

- The BIA assumes that Humatrope® is listed as a Limited Coverage drug for all adult patients above the age of 20 years experiencing GH deficiency.
- The budget impact is measured in terms of incremental costs to PharmaCare which are calculated annually over a three-year period.
- The budget impact analysis is based on the projected growth of adult patients requiring GH therapy as a result of adult and childhood onset deficiency.
- The BIA assumes that all adult PharmaCare patients currently on comparator drugs will switch to Humatrope® once listed.
- Given that Humatrope® will be the first drug to be covered by PharmaCare for adult patients above the age of 20 years experiencing growth hormone deficiency, the BIA assumes that all PharmaCare registered patients currently on GH deficiency drugs will be approved for coverage by PharmaCare Special Authority.
- The BIA assumes constant drug prices for the three-year period considered.

Table 3: Budget Impact Analysis

	FY10/11	FY11/12	FY12/13
Adult Growth Hormone Patients			
# of Patients (19% patient population growth)[1]	125	149	178
Cost per Patient [2]	$11,946	$11,946	$11,946
Paid to Accepted Ratio of 70%[3]	$8,410	$8,410	$8,410
Budget Impact to PharmaCare			
Total Cost paid for by PharmaCare	$1,055,000	$1,256,000	$1,494,000

Note: All final costs are rounded up to nearest 1,000.

BIA Assumptions:

1. 19% growth based on the growth rate in the BC GH treatment population from December 2008 to November 2009. Patient numbers based on the number of PharmaCare registered patients.
2. Cost per Patient is based on average cost per day for Humatrope® patients of $32.73 multiplied by 365 days.

3. 70% paid to accepted ratio is calculated to adjust the $11,946 annual cost to current somatropin patients for adult GH deficiency to PharmaCare deductibles and co-pays given patients' expenditures on other benefit drugs for the entire 2009 benefit year.

Summary and Limitations:

Table 4 summarises the estimated PharmaCare budget impact from listing Humatrope® as a limited coverage drug for all patients above the 20 years of age requiring GH treatment due to GH deficiency.

Table 4: Summary of PharmaCare BIA Results for Humatrope®

Budget Impact	FY10/11	FY11/12	FY12/13	3-Year Total
Total	**$1,055,000**	**$1,256,000**	**$1,494,000**	**$3,805,000**

Note: All final costs are rounded up to nearest 1,000.

The total 3-year budget impact associated with listing Humatrope® as a Limited Coverage drug for the treatment of growth hormone deficiency is estimated to be $3.8 million.

The estimate assumes the coverage of all adult PharmaCare patients requiring GH therapy and should be regarded as a conservative estimate of actual expenditure.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Somatropin (Humatrope®)
Eli Lilly Canada Inc.

Description:

Drug review of somatropin (Humatrope) resubmission for the following:

> For the replacement for endogenous growth hormone in adults with growth hormone deficiency.

Dosage Forms:

5 mg vial
6 mg cartridge
12 mg cartridge
24 mg cartridge

Recommendation:

The Drug Benefit Council (DBC) recommends that somatropin (Humatrope) not be listed.

Reasons for the Recommendation:

1. **Clinical Efficacy and Safety**

- A literature review identified five double-blind, randomized controlled trials (RCTs), comparing somatropin to placebo.
- While there appears to be some effect on some surrogate measures, the clinical outcomes of mortality, morbidity, or quality of life were considered to be more important.
- Based on the available evidence, there is insufficient evidence that somatropin provides therapeutic advantage in terms of mortality, morbidity, or quality of life compared to placebo.
- Due to lack of long term data, there is insufficient evidence to comment on the potential effects of somatropin on cardiovascular event risk reduction. In the RCTs, somatropin was associated with higher incidence of edema and peripheral edema then placebo. There is insufficient long-term data available to link somatropin to development of malignancies.

2. Economic Considerations

- The DBC feels that cost of somatropin is not justified in light of the limited available evidence.

THERAPEUTICS INITIATIVE
Confidential draft

Human Growth Hormone (Humatrope®)
Growth Hormone Deficiency in Adults

March 2010

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Executive Summary

A systematic review of Human Growth Hormone (Humatrope®) for adult patients with growth hormone deficiency (GHD)

Introduction: The manufacturer requests that Humatrope® (generic name: somatropin) be reimbursed in the BC Pharmacare Plans for it's new licensed indication.

Indication: Humatrope is indicated for replacement of endogenous growth hormone in **adults** with growth hormone deficiency, who meet either of the following criteria:

- Adult-onset: patients must have somatropin deficiency syndrome, either alone or associated with multiple hormone deficiencies (hypo pituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
- Childhood-onset: patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Growth Hormone deficiency: The estimated prevalence of GHD in adults is 2 per 10,000 (about half from childhood onset, half from adult onset, mainly pituitary tumors). The incidence of pituitary tumors is ~1 per 100,000 per year. Some of the clinical effects of GH deficiency in adults include: impaired quality of life and psychological well being (i.e. lack of energy, tiredness, emotional lability, reduced sleep), as well as multiple anatomical, physiological and biochemical abnormalities.

Research question:

In double-blinded, randomized controlled trials does Humatrope® (generic name somatropin) provide therapeutic advantage in terms of mortality, morbidity or quality of life over other biosynthetic human growth hormone products or compared with placebo in the treatment of adults with adult or childhood-onset growth hormone deficiency?

Assessment principles:

Double blind randomized controlled trials in adult patients with a diagnosis of GH deficiency, both adult and childhood onset comparing humatrope vs. nutropin®, saizen®, or omnitrope™ (all 3 available in Canada), or genotropin®, norditropin®, zomacton® (all 3 available in the USA), or any other brand of rhGH or placebo will be included. Active comparator trials will be critically appraised and trials versus placebo will be summarized.

Health Outcomes will be assessed using the following hierarchy:

1) All-cause Mortality
2) Non-fatal serious adverse events (SAEs) i.e. cardiovascular, fractures, tumour recurrences
3) General health and social functioning measured using various standard quality of life (QoL) scores
4) Efficacy as measured by changes in exercise endurance and muscle strength.
5) Withdrawals due to adverse events (WDAEs)
6) Other adverse events.

Search strategy: The Cochrane database of systematic reviews and RCTs (to January 19, 2010), EMBASE (1980-January 19, 2010) and MEDLINE (1966-January 19, 2010) were searched.

Findings
Humatrope vs. other brands of rhGH: no DB RCTs identified
Humatrope vs. Placebo: 5 DB RCTs

Overall summary:

No RCT was identified that compared Humatrope to other HGHs

Five DB RCTs compared humatrope to placebo, included 20 to 165 patients and 4 RCTS lasted for 6 months and one RCT was 24 months duration. Two of the trials reported on mortality (as none) and 2 reported on quality of life (Short Form-36 questionnaire was not significantly different than placebo in one trial and Nottingham Health Profile social isolation and physical mobility subscales were significantly better than placebo in one trial [p<0.01].

In all 5 RCTs, Humatrope showed statistically significant improvement in various anatomical and biochemical measures compared to baseline values. There were significant improvements in lean body mass in 3 trials; the largest of them with 165 patients (Chipman 1997) showed a mean increase of approximately 3.6 kg versus the placebo group which lost 0.22 kg, $p < 0.001$). In 4 trials, loss of body fat was significant with GH therapy – by as much as 10.5% vs. 0.4% on placebo in the Chihara 2004 trial. The lipids profile was measured in 3 trials but only attained a level of significance in 2 of the trials, which examined patients separately in accordance with age of GHD onset. Further examination of these subgroups showed that only those patients with adult-onset GHD had significant improvements in HDL-cholesterol (+8.9 mg/dL vs. +4.4 mg/dL placebo, $P < 0.05$; Chipman 1997), LDL-cholesterol (-19.3 mg/dL vs. +7.3 mg/dL placebo, $P \leq 0.01$; Chihara 2004), and total cholesterol levels (-26.7 mg/dL vs. +2.3 mg/dL placebo, $P \leq 0.01$; Chihara 2004) (p = not statistically sig. vs. placebo in childhood-onset group). Exercise capacity was measured in 3 trials but improvement was demonstrated in only a subset of 20 patients with childhood-onset GHD from the largest trial (Chipman 1997). Bone mineral density was improved in one trial (Snyder 2007), increasing by 2.9% in the lumbar spine of patients receiving GH treatment compared to 1.4% in the placebo group ($p< 0.05$). One of the most common markers clinicians use to detect the effectiveness of GH replacement because it roughly parallels GH levels and which has many of the same catabolic effects on the body as GH is the insulin-like growth factor or IGF-I. All 5 RCTs reported increases of IGF-I levels in the serum of patients receiving GH, ranging from approximately 89 to 241µg/L in 3 trials, and in the other 2 trials nearing or exceeding normalization in comparison to a reference (SD score between -0.18 and +3.2). The clinical significance of these changes is not known.

Only 3 trials (Chipman 1997, Chihara 2005, and Snyder 2007) reported adverse events. Meta-analysis of adverse effects was done using RevMan 5.0 of the Cochrane collaboration. Edema (2 trials, RR with 95% CI 3.6 (.2 to 10.5); peripheral edema (2 trials, RR with 95% CI: 10.4 (2.0 to 54.1) are commonly associated with GH and were significantly increased compared to patients receiving placebo. Arthralgia (2 trials, RR with 95% CI: 2.3 (0.9 to 6.1); paraesthesia (2 trials, RR with 95% CI 5.0 (0.9 to 27.9) and headache (2 trials, RR with 95% CI: 1.3 (0.6 to 3.1) did not significantly differ from placebo group.

Conclusions:

- There is insufficient evidence that Humatrope provides a therapeutic advantage in terms of mortality, morbidity or QoL over other biosynthetic human growth hormone products or compared with placebo in the treatment of adults with adult- or childhood-onset growth hormone deficiency.

- No controlled studies establish the appropriate long-term dose of synthetic GH or the serious morbidity and mortality benefit or harm of long term GH replacement in adults.

A systematic review of Human Growth Hormone (Humatrope®) in the treatment of adult patients with growth hormone deficiency (GHD)

1. **REQUEST:** The manufacturer requests that Humatrope® (generic name: somatropin) be recommended for reimbursement under the BC Pharmacare plan for its new indication.

2. DRUG: (Product Monograph)

A. CATEGORIZATION: member of the class of human growth hormones produced by recombinant DNA technology

B. INDICATIONS (From Product Monograph August, 2009):
Previous indication: Humatrope® (generic name: somatropin) is a recombinant human growth hormone (rhGH) indicated for the treatment of growth hormone deficiency, Turner syndrome, idiopathic short stature, and short stature homeobox-containing gene (SHOX) deficiency in children.

New indication: "Humatrope is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency, who meet either of the following criteria:

1. Adult-onset: patients must have somatropin deficiency syndrome, either alone or associated with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or,
2. Childhood-onset: patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes."

A full diagnosis of adult growth hormone deficiency (GHD) normally requires the appropriate growth hormone stimulation test except where there is evidence of congenital or genetic GHD or multiple pituitary hormone deficiencies due to organic disease.

C. Drug Route, Form and Strength (Product Monograph)

1) Lyophilized powder in 2 and 5mg vials reconstituted with 1.5 to 5mL solution of water, metacresol and glycerin (a Humatrope diluent)
2) Cartridges of 6, 12, and 24mg of lyophilized powder reconstituted using an accompanying syringe pre-filled with 3.15mL of the Humatrope diluent. Reconstituted cartridge is then attached to an injector pen (HumatroPen).

D. RECOMMENDED DOSE: (From Product Monograph August, 2009)
Adult Growth Hormone Deficiency
At the start of therapy, the dose is not to exceed 0.006 mg/kg/day given subcutaneously at rotated injection sites. The dose may be increased to a maximum of 0.0125 mg/kg/day depending upon tolerability and meeting targets for age- and sex-matched IGF-I concentrations. Dosage regimen is individualized for each patient.

Note: higher doses may be required for women who are estrogen-replete or are taking oral estrogen, and lower doses for older and obese patients.

The Humatrope diluent can be replaced with sterile water intended for injection if the patient develops sensitivity to it.

E. DURATION OF THERAPY: duration not specified.

F. MECHANISM OF ACTION (From Product Monograph August, 2009)
Humatrope is a recombinant polypeptide that is identical in structure to pituitary-derived human growth hormone. It is biosynthesized from the DNA of E. coli bacteria containing a modified gene for human growth hormone.

Humatrope acts in the same way as pituitary-derived human growth hormone in that both or either stimulate skeletal bone and muscle growth, increase cellular protein synthesis (serum urea nitrogen levels are reduced with rhGH), and they have direct effects on carbohydrate metabolism, lipid metabolism, and mineral metabolism. For adults with growth hormone deficiency (GHD) acquired from childhood or as an adult these results translate into improvements in body composition and exercise capacity, normalized HDL cholesterol, and improvements in physical mobility as well as reduced social isolation (data from placebo-controlled trials).

G. PHARMACOKINETICS (From Product Monograph August, 2009)
In vitro studies have shown that Humatrope is pharmacokinetically equivalent to pituitary-derived human growth hormone. In healthy subjects, the bioavailability of Humatrope is 75% and 63% via subcutaneous and intra-muscular injection. It is metabolized by the liver and kidneys and eliminated at a rate of 0.14 L/hr/kg. The mean half-life is 3.8 and 4.9 hours, respectively following subcutaneous and intra-muscular administration. Urinary excretion of Humatrope has not been measured.

H. CONTRAINDICATIONS (From Product Monograph August, 2009)
Humatrope is contraindicated in patients with acute critical illness as the result of the complications following open heart or abdominal surgery, multiple accidental traumas or to patients having acute respiratory failure.
It is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.
If there is evidence of active malignancy, treatment with Humatrope must not start or should be stopped. Sensitivity to the Humatrope solution, metacresol or glycerin requires a switch to water as the diluent.

I. Warnings and Precautions (From Product Monograph August, 2009)
General
Acute Critical Illness: Mortality increased significantly (42%) versus placebo (19%) in 522 acutely ill, non-GH deficient adults treated with GH due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. Patients received between 5.3 and 8.0 mg of GH daily.
The site of subcutaneous injection should be rotated to prevent lipo-atrophy from occurring.

Endocrine & Metabolism
GH may induce insulin resistance in diabetic patients, therefore the manufacturer recommends closely monitoring such patients and if necessary to adjust the dose of insulin. Monitoring is also recommended for patients with multiple hormonal deficiencies who are on standard hormone replacement therapy because of possible cases of hypothyroidism from the addition of GH.

Sensitivity/Resistance
A switch to water is requested if there is sensitivity to the Humatrope diluents. The peptide structure of GH may cause some patients to develop antibodies, which requires testing if there is a lack of response to therapy.

Before GH replacement is continued into adulthood in patients previously treated for childhood-onset GHD, the maintenance and regimen of treatment should be re-evaluated.

The manufacturer comments that data on prolonged GH treatment in adults is limited, but post-marketing studies thus far have reported cases involving arthralgia, peripheral edema, myalgia, carpal tunnel syndrome, paraesthesia, dyspnea, hypertension, and sleep apnea. Patients over 40 years of age reported carpal tunnel syndrome more frequently than in younger patients.

Although fertility and nursing studies in animals have not been performed, GH is not recommended in pregnant or nursing women.

The elderly (< 60 years of age) may be more vulnerable to adverse effects than other patients when given GH based on body weight.

J. Adverse Reactions (From Product Monograph August, 2009)
Results from controlled, blinded trials show that GHD adults experience more frequent edema (17% vs. 4.4%) and peripheral edema (11.5% vs. 0%) with GH than with a placebo. Treatment-emergent adverse events reported over an 18-month period as possibly related to GH replacement therapy include carpal tunnel syndrome, edema, arthralgia, paraesthesia, hypesthesia, myalgia, peripheral edema, back pain, headache, and joint disorder.

3. Background

A. NATURAL HISTORY OF THE DISEASE

The estimated prevalence of GHD in the adult population is 2 per 10,000 (about half from childhood onset, half from adult onset, mainly pituitary tumors). The incidence of pituitary tumors is ~1 per 100,000 per year. GH is synthesized and released from the anterior pituitary gland and is under control of GH releasing hormone (GHRH) which stimulates GH secretion, and, somatostatin which inhibits GH secretion.

Endogenous GH secretion is pulsatile and is influenced by age, sex, sex hormones, body composition, physical activity, and fasting state, and after peaking in puberty, declines with age by approximately 14% per decade (Fisker 2005). Two groups of patients have been identified as at risk of GHD; adults who have had injury to the hypothalamic/pituitary axis either a pituitary or suprasellar tumor,

pituitary surgery, radiotherapy, or idiopathic; and those with childhood-onset GH deficiency who received GH replacement therapy as children (Toogood 2005).

Unlike childhood-onset GHD where the key symptom is retarded growth, adult-onset GHD lacks a specific symptom required for diagnosis of GHD. Some of the clinical effects of GH deficiency in adults include: impaired quality of life and psychological well-being (i.e. lack of energy, tiredness, emotional lability, reduced sleep), abnormal body composition (increased fat mass, decreased lean body mass, decreased total body water, increased abdominal adiposity), decreased bone mineral density, reduced exercise capacity and muscle strength, abnormal EKG (reduced cardiac size and left ventricular wall thickness), serum lipid abnormalities (raised LDL cholesterol, total cholesterol, and triglycerides, reduced HDL cholesterol), hypertension, reduced insulin sensitivity, abnormal cardiovascular risk factors (raised C-reactive protein and interleukin-6, impaired fibrinolysis, increased carotid intima media thickness), thin skin, decreased sweating, reduced red cell mass, and reduced glomerular filtration rate (Toogood 2005).

In England and Wales, NICE guidelines for the use of rhGH were drafted targeting patients for GH therapy who have known hypothalamic-pituitary abnormality (e.g. adenoma, radiotherapy, head injury), a peak GH response of < 3ng/mL during an insulin tolerance test or equivalent alternative test, and an impaired quality of life (a score of ≥11 QoL-AGHDA) (Toogood 2005). Therapy is aimed at proper dose titration and long-term follow-up.

Increased mortality, including excess cardiovascular and cancer mortality and morbidity relative to background population rates, has been described in cohorts of adults with GHD (Svensson 2004). A Swedish retrospective analysis included hypo pituitary patients who had received inpatient care between 1987-1992 (n=1411). Mortality rates to 1994 were compared with background population rates. GH replacement was not used in Sweden at this time, except within a research setting. Mortality rates were higher than expected: RR with 95% CI =3.8 (3.4-4.2); there were more malignancies, fatal and nonfatal: RR with 95% CI =1.8 (1.5-2.2), and cancer of the colon and rectum was increased. Myocardial infarction rates were also higher, but only if fatal events outside of hospital were included: RR with 95% CI =1.4 (1.1-1.8), and cerebrovascular events were increased: RR with 95% CI = 2.7 (2.2-3.4).

Svensson et al. also carried out a prospective cohort study of GH-treated hypo pituitary adults (n=289) and did not find increases in mortality or cardiovascular events and cancer. However, bias in selection for treatment is likely to have influenced results.

There is no randomized controlled trial evidence of effects of GH replacement on mortality or cardiovascular or cancer morbidity, and trials typically end within a maximum of 12 to 21 months, at best. GH therapy may in rare instances, increase cardiovascular complications such as hypertension and atrial fibrillation (Christ 1997). There have also been reports of encephalocele, and headache with tinnitus, but with cessation of GH therapy these symptoms have invariably improved.

Summary of available systematic reviews and meta-analyses

Exercise Capacity

Rubeck et al 2009 is a systematic review of the effects of GH on exercise capacity and muscle strength in GH-deficient adults. 15 double-blinded, randomized, placebo-controlled trials (published between 1989 and 2007) containing either outcomes on aerobic exercise capacity, muscle strength, and/or muscle mass were included. A total of 306 patients treated with GH or placebo for between 3 and 12 months were included in the analysis. The overall effect of GH on exercise capacity measured in percentage change was a significant weighted mean difference (vs. placebo) of +8.94% (95% CIs 7.42 to 10.45). Maximal oxygen uptake (VO_2 max), a measure of exercise capacity also increased with GH treatment by a WMD of +0.17 liters per minute (95% CIs 0.13 to 0.20). Mean muscle volume also increased significantly by 7.1 ± 1.6% ($p < 0.001$ vs. placebo) based on a meta-analysis of 4 out of 15 of the trials. GH had no effect on muscle strength, however, expressed in terms of percent change compared with placebo (WMD: +3.24% (95% CIs: -1.12 to 7.60).

Widdowson et al 2008 investigated exercise capacity based on measurement of VO_2 max, maximal power output, and maximal heart rate from 11 DB RCTs (all placebo-controlled; N=268, trials ranged from 6 to 18 months in duration), the majority of which were cited by the Rubeck et al 2009 review above. Maximum power output and VO_2 max were significantly improved with GH treatment compared to placebo (effect sizes were +0.4 and +0.34; 95% CIs 0.06 to 0.74 and 0.07 to 0.62, respectively), whereas maximum heart rate did not change (p=NS). Accounting for all three measures combined, GH showed an overall effect on exercise capacity that was statistically significant (effect size 0.32; 95%CIs: 0.08 to 0.56).

Cognitive Function

Deficits in cognitive function (revealed by neuropsychological testing) associated with GHD and the effects of GH on cognition were examined in adults 16 to 77 years of age (**Falleti 2006**). **5 cross-sectional studies** consisting of 164 patients with untreated GHD and 74 healthy control subjects, and 9 prospective and/or cross-sectional studies consisting of 219 patients with GHD who were to receive either GH replacement or a control for between 3 months to up to 16 years were included in the analysis (published between 1989 and Nov. 2004). Compared to controls, GHD patients had impaired cognition in three domains: attention (weighted effect size: -1.46 vs. control), memory (ES: -0.46), and executive function (ES: -0.64). The differences were much less significant when GHD patients were compared to a standard reference (i.e. normative data). Even after treatment with GH for periods of up to 16 years, patients performed worse on attention (ES: -0.79 vs. control), memory (ES: -0.90), and executive function (ES: -0.23) than their controls. Although, within the GH group of patients itself compared to baseline, cognitive function continually improved at each successive time point for attention, memory, and spatial ability up to the last available point, whereas motor and executive function did not. The authors commented that effect sizes greater than 0.5 (moderate change) are clinically significant.

Arwert et al 2005 is a meta-analysis of studies (placebo-controlled, cross-over/parallel or open-label trials published between 1985 and Jan. 2004) investigating growth hormone's effect on patient-reported outcomes and cognitive functioning in adults with GHD. A standard effect size was derived from the pooling of results from various patient-reported tests or questionnaires such as the Nottingham Health Profile (NHP), Psychological General Well Being Schedule (PGWB), QoL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA), General Health Questionnaire (GHQ), Hopkins Symptom Checklist (HSCL) from 15 studies as well as neuropsychological tests from 4 studies involving a total of 830 patients over a duration of 3 months to a maximum of 50 months. After 6 months of observation, patients receiving GH experienced improvements in their quality of life, health status, and psychological well-being compared to baseline (effect size [d]: 0.55 CIs: 0.31 to 0.79; $p < 0.001$), ***but not when compared to placebo*** (effect size [d]: -0.075 CIs: -0.32 to 0.17; p=NS). Patients receiving GH for 6 months also did not experience any improvement in cognitive functioning (effect size: 0.29 CIs: -0.18 to 0.77, p=NS) compared to baseline. The authors defined a small effect as an effect size between 0.2 and 0.4, a medium effect: 0.5 to 0.7, and a large effect: 0.8 or higher. There are several limitations to this review including the fact that comparison to placebo was not performed for the cognitive outcome due to lack of sufficient number of trials to meta-analyze.

Cardiovascular Risk Factors

The **Maison et al 2004** meta-analysis assessed the effect of GH replacement on cardiovascular risk factors in GHD adults (Maison et al, 2004). Thirty-six double blind and one single blind randomized, placebo-controlled trials ranging in duration from 1 week to 18 months, published up to Aug. 2003 were included in the analysis totaling 1377 patients. Compared to placebo, GH treatment was associated with statistically significant increases in lean body mass (by a weighted mean difference of +2.74 kg vs. placebo), insulin (WMD +8.66pmol/L) and glucose (WMD +0.22mmol/L) levels; significant reductions were observed in fat mass (WMD -3.05 kg), LDL-cholesterol (WMD -0.53mmol/L), total cholesterol (-0.34mmol/L), and diastolic blood pressure (WMD -1.80 mm Hg). There were no changes (P=NS) in body mass index, triglycerides, HDL-cholesterol, or systolic blood pressure. A subgroup analysis of low (≤0.35 U/kg/week) versus high (>0.5 U/kg/week) doses of GH indicated a dose-dependent effect on fat mass only. Low doses of GH had more significant, positive effects on 7 cardiac parameters (lean body mass, fat mass, diastolic BP, LDL-cholesterol, total cholesterol, glucose, and insulin) than did the high doses. A longer duration of therapy (≥ 6 months) was also associated with significant, positive effects on all 7 cardiac parameters listed above compared to a shorter duration of therapy (< 6 months). Some differences in effect were also seen in male patients compared to females, older patients compared to their younger counterparts, and adult- vs. childhood- onset GHD patients.

Cardiac Structure and Function

A 2003 systematic review (**Maison et al 2003**) investigated the effects of GH on cardiac structure and function in GHD adults measured using 2-dimensional echocardiography. 16 randomized placebo-controlled trials, 9 of them blinded, and 7 open-label comprising 468 patients (duration of trials was between 3 and 36 months) were included. In patients receiving GH treatment there was a statistically

significant increase in left ventricular mass (weighted mean difference vs. control was +10.8 grams, p = 0.02), interventricular septum thickness (WMD +0.28mm, p < 0.001), left ventricular end-diastolic diameter (WMD +1.34mm, p < 0.001), and stroke volume (WMD +10.3mL, p < 0.001) compared to control. GH treatment had no effect (p=NS vs. control) on left ventricular posterior wall thickness, left ventricular end-systolic diameter, ratio of E-wave and A-wave peak velocities of the mitral flow profile, isovolumic relaxation time, or fractional shortening compared to the control. The authors commented that improvement in cardiac function might be implicated in the increase observed in exercise performance with GH treatment.

Quality of Life

A UK National Health Service Health Technology Assessment report on the clinical effectiveness and cost effectiveness of growth hormone in adults was published in 2002 (**Bryant 2002a**). The main aim of this systematic review was to assess the impact of growth hormone replacement on quality of life (QoL) in adults with severe GHD, either of childhood or adult onset. ***The rationale for assessing the quality of life outcome was its immediate relevance to patients (versus surrogate markers that may indicate elevated risk for future disease)***. Impaired quality of life is a frequent indicator for GH replacement. Medline and EMBASE were searched up to May 2001 yielding seventeen RCTs (N=892 patients) in which several different validated QoL instruments were used (4 most frequent: GHQ, HDS, NHP, PGWB, and 19 other scales, which are typically self-reporting measures used to evaluate QoL).

Longer-term Observational Studies

At least 8 open-label, non-randomized observational studies of 3 years (Attanasio 2002), 5 years (Gotherstrom 2001, Svensson 2003, Bravenboer 2005, Colao 2008), 7 years (Svensson 2002, van der Klaauw 2006), and up to 10 years in duration (Gotherstrom 2007) have assessed the effects of GH in GHD adults on various outcomes, most of them biochemical surrogate markers, anthropometric indexes (i.e. body-mass index, body weight, height, waist circumference), body composition, muscle strength, bone mineral density and content, bone metabolism, cardiac structure and function and other cardiovascular risk factors which are expected to improve with therapy.

Quality of life (Koltowska-Haggstrom 2006) in 1686 severe GHD adults on GH replacement therapy (KIMS Pfizer International metabolic database) was initially very poor when compared to 4480 cohorts from the general population (obtained through surveys, questionnaires, and interviews), but improved significantly, and was normalized by the end of follow-up which was different for each country (in England & Wales it was 7 years, Spain 4 years, Netherlands 6 years, and Sweden 8 years). The greatest improvement occurred during the first year of treatment with GH. Measurements were made using the Quality of Life-Assessment for Growth Hormone Deficiency in Adults (QoL-AGHDA) which contains 5 dimensions all of which improved - in order of shortest time it took to reach normal population levels to the longest, regardless of country of origin: social isolation, tenseness, problems with self-confidence, tiredness, and memory and concentration problems.

A new QoL instrument, the QLS-H or Questions on Life Satisfaction questionnaire is being developed and validated to address the specific problems of adults with growth hormone deficiency compared to more general scores like the SF-36 and

NHP (Blum 2003). Questions are weighted according to the importance they have with the individual. An observational study which used the QLS-H to assess the effects of GH replacement in GHD adults (Rosario et al, 2004) showed that within one year of being on GH treatment, patients experienced significant improvements in their quality of life such that their Z-scores were normalized and remained relatively stable for the next 3 years (from graph). Amongst adult-onset patients, the youngest age bracket (< 25 years of age) had above normal Z-scores within the 1st year.

Results from a 3-year, open-label study (Svensson 2004a), which examined the quality of life in 237 Swedish adults with GHD, indicate significant effects associated with GH replacement (Genotropin product in use). Both the Psychological General Well-Being index (PGWB) and the QoL-AGHDA showed significant improvement within the 1st year, and a sustained response throughout the remaining 2 years of the study. The PGWB decreased from 8.4 at baseline to 4.8 at the study's endpoint ($P < 0.01$), while the QoL-AGHDA increased from 73.2 at baseline to 82.1 at endpoint ($P < 0.01$). The number of visits to the doctor and days in hospital in the previous year, leisure time physical activity, and satisfaction with physical activity all improved.

B. GOAL OF THERAPY

Most literature state that the goal of therapy in adult-onset GHD is to improve body composition, maintain skeletal mass, normalize cardiovascular risk factors, stabilize IGF-I levels within a given range, and to enhance physical and psychosocial functioning. In adults with childhood-onset GHD the goal of therapy is to achieve full somatic development (i.e. accrual of muscle and bone mass).

C. AVAILABLE TREATMENTS

For the approved indication covered in this review, other recombinant human growth hormone available in Canada are Nutropin®, Saizen®, Omnitrope™ and Humatrope®.

D. CANADIAN GUIDELINES

Endocrinologists first developed Canadian guidelines for the management of adult growth hormone deficiency in 2006 (Ur et al 2006). ***The guidelines, which are based on a systematic review of evidence do not advocate for the use of GH to prevent the normal effects of aging in non-GH deficient individuals since the evidence of its efficacy is lacking.***

Growth hormone deficiency (GHD) in adults is diagnosed using a GH stimulation test after the patient presents with a history of childhood-onset GHD, hypothalamic-pituitary disease or surgery, cranial irradiation, or moderate to severe traumatic brain injury. The testing involves the gold standard - insulin (i.e. insulin tolerance) - or clonidine, L-arginine, L-dopa, glucagon, or GH releasing hormone to stimulate the body's GH reserves, which if below the cutoff value of 5µg/L (< 3µg/L for the insulin tolerance test) is indicative of GHD.

According to the evidence gathered from the systematic review, GH replacement has the benefit of improving body composition by increasing lean body muscle mass and decreasing visceral adipose tissue, decreasing LDL cholesterol concentrations, improving cardiac output by up to 40%, reducing the carotid intima

medial thickness, decreasing c-reactive protein and interleukin-6 inflammatory markers, increasing bone mineral density and improving psychological well-being by reducing mental distress and increasing exercise capacity. ***However, the guidelines state that any real benefits of such outcomes on cardiovascular mortality and morbidity are inconclusive due to the lack of sufficient clinical data***.

The optimal dose of GH in adults is not yet defined, but is suggested to be much lower than that used in children for GHD, starting at a dose of 0.0025 mg/kg/day given as a self-administered, subcutaneous injection in the abdomen. Dose titrations of 0.1 mg/day every 2 to 3 months over a 6 to 12 month period (up to a maximum of 0.0125 mg/kg/day) are recommended until patients' symptoms no longer improve; emergence of side effects signifies the initiation of a reduction in dosage. IGF-I concentrations should also extend into the upper half of the normal range for age and sex-matched controls. If there is a clear benefit from treatment with GH in the absence of side effects, then the guidelines support its continued use over the long-term and possibly for the lifetime of the patient. Over time, if the patient feels well but is not improving from GH replacement, has reached the maximal dose and is in the mid to normal IGF-I range, therapy could be discontinued.

E. OUTCOME MEASURES

The following are a list of outcome measures used in the clinical trials reviewed:

- **Health status**: Short-form 36 Questionnaire (SF-36), and Nottingham Health Profile (NHP)
- **Exercise capacity**: VO_2 max, maximal O_2 pulse, maximal power output, time to exhaustion, accumulated work, R-value (respiratory exchange), maximal ventilation, anaerobic threshold, maximal heart rate, blood pressure.
- **Muscle strength and fatigue**: iso-kinetic dynamometry and bicycle ergometry.
- **Body composition**: lean body mass measured using DEXA (dual-energy x-ray absorptiometry), and bioimpedance analysis; fat mass by DEXA or skin folds
- **Serum IGF-I** and IGFBP-3 concentrations (surrogate markers)
- **Cardiovascular parameters**: lipids profile (total cholesterol, LDL and HDL cholesterol, LDL/HDL ratio, triglycerides), glucose and insulin levels, glycosylated hemoglobin
- **Cardiac structure and function** (using echocardiography): interventricular septum thickness (IVS), left ventricular posterior wall thickness (LVPW), left ventricular end-systolic diameter (LV-ESD), LV-EDD (left ventricular end-diastolic diameter), FS (fractional shortening), left ventricular mass (LVM), left atrium mass (LA), LVM/body surface area, aorta outflow tract integral (VTI), AV-plane movement, diastolic closing motion of the mitral valve leaflets (EF slope), rapid filling wave/atrial filling wave (E/A ratio), and pulmonary vein systolic/diastolic wave (S/D ratio).
- **Bone mineral density** (measured using DEXA)
- **Bone metabolism markers** (i.e. osteocalcin, PICP, ALP, U-pyridinoline, BSALP, N-telopeptide/creatinine ratio)
- **Lab values:** thyroxine-T_4, SGOT.

Parameters for testing psychological well-being, quality of life, and cognitive functioning were absent from the trials included in this review but will normally

include the General Health Questionnaire (GHQ) and Well-Being Questionnaire (W-BQ); the hormone deficiency-specific individualized quality of life questionnaire (HDQoL/QoL-AGHDA), and the non-verbal Wechsler Adult Intelligence Scale (WAIS), respectively.

4. RESEARCH QUESTION:

In double-blinded, randomized controlled trials does Humatrope® (generic name somatropin) provide therapeutic advantages in terms of mortality, morbidity or quality of life over other biosynthetic human growth hormone products or compared with placebo in the treatment of adults with adult- or childhood-onset growth hormone deficiency?

5. ASSESSMENT PRINCIPLES:

Study design: double blind randomized controlled trials.
Patients: Adult patients with a diagnosis of GH deficiency, both adult and childhood onset.
Intervention and comparator(s):

a. Humatrope vs. Nutropin®, Saizen®, or Omnitrope™ (all 3 available in Canada), or Bio-tropin, Genotropin®, Norditropin®, Nutropin®, Omnitrope™, Serostim, Saizen, Tev-tropin, Valtropin, or Zorbtive (all 10 available in the USA), or any other brand of rhGH (due to the identical amino acid sequence that the different manufacturers claim to derive their synthetic rhGH products from, it is assumed that the pharmacokinetics will not deviate appreciably between products).
b. Humatrope vs. Placebo

Hierarchy of Health Outcomes

1) All-cause Mortality
2) Non-fatal serious adverse events (SAEs) i.e. cardiovascular, fractures, tumour recurrences
3) General health, social functioning, psychological well-being, and quality of life measured using various standard questionnaires and surveys
4) Efficacy as measured by changes in exercise capacity and muscle strength.
5) Withdrawals due to adverse events (WDAEs)
6) Other adverse events.

6. SEARCH STRATEGY AND SEARCH FINDINGS

A. SEARCH STRATEGY

Comprehensive search

The Cochrane database of systematic reviews and RCTs (to January 19, 2010), EMBASE (1980-January 19, 2010) and MEDLINE (1966-January 19, 2010) were searched.

Key words used for EMBASE/MEDLINE were: “humatrope,” and “randomized/randomised controlled trial”.

Key words used for the Cochrane RCT database were “humatrope” and “adult*.” Full trial reports were included. Abstracts and posters were excluded.

In addition, retrieved clinical trials and some review articles were hand searched for references. The U.S. FDA and EMEA websites were also searched.

B. SEARCH FINDINGS

Humatrope vs. other brands of rhGH: no DB RCTs identified

Humatrope vs. Placebo: 5

1. Nass R, Huber RM, Klauss V, Muller OA, Schopohl J, and Strasburger CJ. Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. Journal of Clinical Endocrinology and Metabolism, 80 (2): 552-557, 1995.
2. Chipman JJ, Attanasio AF, Birkett MA, Bates PC, Webb S, et al. The safety profile of GH replacement therapy in adults. Clinical Endocrinology, 46(4): 473-481, 1997.
    a. Attanasio AF, Lamberts SWJ, Matranga AMC, Birkett MA, Bates PC, Valk NK et al. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Journal of Clinical Endocrinology and Metabolism, 82(1): 82-88, 1997 (Secondary publication).
    b. Gullestad L, Birkeland K, Bjonerheim R, Djoseland O, Trygstad O, Simonsen S. Exercise capacity and hormonal response in adults with childhood onset growth hormone deficiency during long-term somatropin treatment. Growth Hormone and IGF Research, 8(5): 377-384, 1998. (Additional publication).
3. Fernholm R, Bramnert M, Hagg E, Hilding A, Baylink DJ, et al. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. Journal of Clinical Endocrinology & Metabolism, 85(11): 4104-4112, 2000.
    a. Elgzyri T, Castenfors J, Hagg E, Backman C, Thoren M, et al. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. Clinical Endocrinology, 61(1): 113-122, 2004 (Additional publication).
4. Chihara K, Koledova E, Shimatsu A, Kato Y, Kohno H et al. Adult GH deficiency in Japanese patients: Effects of GH treatment in a randomised, placebo-controlled trial. European Journal of Endocrinology, 151(3): 343-350, 2004.
    a. Chihara K et al. An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency. European Journal of Endocrinology, 153: 57-65, 2005. (open-label extension phase).
    b. Urushihara H, Fukuhara S, Tai S, Morita S, and Chihara K. Heterogeneity in responsiveness of perceived quality of life to body composition changes between adult- and childhood-onset Japanese hypopituitary adults with GH deficiency during GH replacement. European Journal of Endocrinology, 156: 637-645, 2007. (Additional publication).
5. Snyder PJ et al. Effect of growth hormone replacement on BMD in adult-onset growth hormone deficiency. Journal of Bone and Mineral Research, 22(5): 762-770, 2007.

Adverse Events from Open-label Trials - 2

1. Shalet S.M. Shavrikova E. Cromer M. Child C.J. Keller E. Zapletalova J. Moshang T. Blum W.F. Chipman J.J. Quigley C.A. Attanasio A.F. Effect of growth hormone (GH) treatment on bone in post-pubertal GH-deficient patients: A 2-year randomized, controlled, dose-ranging study. Journal of Clinical Endocrinology and Metabolism, 88(9): 4124-4129, 2003

a. Attanasio A.F. Shavrikova E. Blum W.F. Cromer M. Child C.J. Paskova M. Lebl J. Chipman J.J. Shalet S.M. Continued Growth Hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. Journal of Clinical Endocrinology and Metabolism. 89(10)(pp 4857-4862), 2004 (additional publication)

2. Eli-Lilly Study B9R-JE-K03A. Extended clinical study of LY137998 [somatropin (recombinant DNA origin)] in adults with growth hormone deficiency. Clinical Trial Registry ID #6018, Summary approved April 24, 2007.

Studies excluded:

- **Humatrope vs. Placebo [cross-over study – no placebo data]:**

1. Bengtsson BA, Eden S, Lonn, L et al. Treatment of adults with growth hormone deficiency with recombinant human growth hormone. Journal of Clinical Endocrinology and Metabolism, 76: 309-317, 1993. (data reported for GH treatment group only).
    a. Stenlof K, Sjostrom L, Lonn L, Bosaeus I, Kvist H, et al. Effects of recombinant human growth hormone on basal metabolic rate in adults with pituitary deficiency. Metabolism: Clinical & Experimental, 44(1): 67-74, 1995. (Additional publication).

- **Humatrope vs. Placebo [withdrawal studies]:**

2. Gibney, J. et al. Effect of growth hormone (GH) on glycerol and free fatty acid metabolism during exhaustive exercise in GH-deficient adults. Journal of Clinical Endocrinology & Metabolism, 88(4): 1792-1797, 2003.
3. McMillan, C.V. et al. Evaluation of two health status measures in adults with growth hormone deficiency. Clinical Endocrinology, 58(4): 436-445, 2003
    a. McMillan, C.V. et al. Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency. Clinical Endocrinology, 59(4): 467-475, 2003. (Additional publication).

- **Humatrope dose ranging trials:**

4. Kehely A, Bates PC, Frewer P, Birkett M, Blum WF et al. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: A comparison of two dosage algorithms. Journal of Clinical Endocrinology and Metabolism. 87(5): 1974-1979, 2002. (Low vs. conventional doses)
    a. Burt MG, Gibney J, Hoffman DM, Margot Umpleby A, and Ho KKY. Relationship between GH-induced metabolic changes and changes in body composition: A dose and time course study in GH-deficient adults. Growth Hormone and IGF Research. 18(1): 55-64, 2008.
5. Hoffman AR, Strasburger CJ, Zagar A, Blum WF, and Kehely A. Efficacy and tolerability of an individualized dosing regimen for adult growth hormone replacement therapy in comparison with fixed body weight-based dosing. Journal of Clinical Endocrinology and Metabolism. 89(7): 3224-3233, 2004 (open-label, fixed vs. individualized doses).
    b. Hartman ML, Weltman A, Zagar A, Qualy RL, Hoffman AR, et al. Growth hormone replacement therapy in adults with growth hormone deficiency improves maximal oxygen consumption independently of dosing regimen or physical activity. Journal of Clinical Endocrinology and Metabolism. 93(1): 125-130, 2008.

- **Combination therapy with Humatrope**

6. Johannsson G, Gibney J, Wolthers T, Leung K-C, and Ho KKY. Independent and combined effects of testosterone and growth hormone on extracellular water in hypopituitary men. Journal of Clinical Endocrinology and Metabolism. 90(7): 3989-3994, 2005. (GH + testosterone vs. GH).

Systematic Reviews - rhGH vs. Placebo: 7

1. Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, et al. Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation. Health Technology Assessment, 6(19): 1-104, 2002a.
    a. Bryant J. Loveman E. Cave C. Chase D. and Milne R. Endocrinology trial design: Adverse event reporting in randomised controlled trials of recombinant human GH in GH-deficient adults. Journal of Endocrinology. 175(2): 545-552, 2002.
2. Maison P and Chanson P. Cardiac Effects of Growth Hormone in Adults with Growth Hormone Deficiency: A Meta-Analysis. Circulation. 108(21): 2648-2652, 2003.
3. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B et al. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. Journal of Clinical Endocrinology & Metabolism, 89(5): 2192-2199, 2004.
4. Arwert LI, Deijen JB, Witlox J, and Drent ML. The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: A meta-analysis. Growth Hormone and IGF Research. 15(1): 47-54, 2005.
5. Falleti MG, Maruff P, Burman P, and Harris A. The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: A meta-analysis of the current literature. Psychoneuroendocrinology. 31(6): 681-691, 2006.
6. Widdowson WM, and Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: A meta-analysis. Journal of Clinical Endrocrinology and Metabolism, 93 (11): 4413-4417, 2008.
7. Rubeck KZ, Bertelsen S, Vestergaard P, and Jorgensen JOL. Impact of GH substitution on exercise capacity and muscle strength in GH-deficient adults: A meta-analysis of blinded, placebo-controlled trials. Clinical Endocrinology. 71(6): 860-866, 2009.

7. CRITICAL APPRAISAL OF INCLUDED TRIALS:

No RCT compared Humatrope to other brands of rhGH available in Canada.

8. SUMMARY OF TRIALS COMPARING HUMATROPE vs. PLACEBO

Refer to Appendix A and B for details.

9. ADDITIONAL INFORMATION ON ADVERSE EVENTS

Safety Considerations

1. **Formation of antibodies**

   The risk of developing antibodies to exogenous protein is well known when treating with biological medications. The risk of developing antibodies to GH when treated with Humatrope® was estimated to be 1.6% in the first 6 months of

treatment with Humatrope®. The effect of the presence of antibodies on the effect of the drug is unknown. In children the phenomenon had no effect on growth (Pirazzoli 1995). Please note the lack of validation of the anti GH antibody assay (EMEA 2006).

2. **Induction of diabetes**

A reduction in insulin sensitivity is known to occur during the first 12 months of treatment with GH. Later it appears to return to baseline levels. In an open label study following 90 patients treated with GH (Genotropin®, a dose titration regimen to maintain serum IGF-I levels restricted to the upper half of the normal range), there was a significant rise in fasting circulating glucose after 6 months of treatment (from baseline fasting plasma glucose of 4.72 ± 0.06 to 5.15 ± 0.70) and after 24 months (5.44 ± 0.41, 25 patients). An increase in glycosylated hemoglobin was also observed (baseline 4.9 ± 0.05, 6 months 5.07 ± 0.06, 24 months 5.19 ± 0.3 {24 months- 22 patients); normal range 3.7-5.1%). One patient developed diabetes and required oral hypoglycemic agents (Florakis 2000).

3. **Hypothyroidism**

Chronic GH replacement therapy has been suggested to unmask central hypothyroidism. There is controversial evidence whether GH replacement therapy is associated with hypothyroidism (Porretti 2002; Agha 2007; Amato 1996). In a study published in 2008, treatment with Humatrope® (49 patients, median follow up 2 years) there was a small but significant decrease in free T4 , although it remained in the normal range (results presented as a graph). Three patients were either diagnosed with hypothyroidism or had to increase their dose of thyroid replacement therapy (in hypothyroidic patients [Losa 2008]).

4. **The risk of developing malignancy**

Concerns that treatment with GH may be associated with increased risk of malignancy have arisen because of the suspected association between markers of high GH levels in acromegalic patients and incidence of malignancy (especially colo-rectal malignancy). However, acromegaly may not be associated with increased risk of colo-rectal malignancy (Renehan 2000), and currently there is no evidence that treatment with FH is associated with increased risk.

KIMS is a pharmaco-epidemiological registry - Pfizer International Metabolic Database for assessing long-term clinical and safety outcomes of GH treatment (Genotropin®) in patients with GH deficiency. A 10-year analysis demonstrated no increase in the risk for tumors in adults receiving GH replacement. 6428 patients enrolled in that database, representing 14,073 treatment years, reported 118 tumors in 115 patients, not significantly increased from the number of tumors expected in this population. The number of cranial tumors and skin cancers were increased, maybe due to close follow up of the patients (Svensson and Bengtsson 2004).

10. OVERALL SUMMARY

No RCT was identified that compared Humatrope to other HGHs

Five DB RCTs compared humatrope to placebo, included 20 to 165 patients and 4 RCTS lasted for 6 months and one RCT was 24 months duration. Two of the trials reported on mortality (as none) and 2 reported on quality of life (Short Form-36 questionnaire was not significantly different than placebo in one trial and Nottingham Health Profile social isolation and physical mobility subscales were significantly better than placebo in one trial [p<0.01].

In all 5 RCTs, Humatrope showed statistically significant improvement in various anatomical and biochemical measures compared to baseline values. There were significant improvements in lean body mass in 3 trials; the largest of them with 165 patients (Chipman 1997) showed a mean increase of approximately 3.6 kg versus the placebo group which lost 0.22 kg, p < 0.001). In 4 trials, loss of body fat was significant with GH therapy – by as much as 10.5% vs. 0.4% on placebo in the Chihara 2004 trial. The lipids profile was measured in 3 trials but only attained a level of significance in 2 of the trials, which examined patients separately in accordance with age of GHD onset. Further examination of these subgroups showed that only those patients with adult-onset GHD had significant improvements in HDL-cholesterol (+8.9 mg/dL vs. +4.4 mg/dL placebo, P < 0.05; Chipman 1997), LDL-cholesterol (-19.3 mg/dL vs. +7.3 mg/dL placebo, P ≤ 0.01; Chihara 2004), and total cholesterol levels (-26.7 mg/dL vs. +2.3 mg/dL placebo, P ≤ 0.01; Chihara 2004) (p = not statistically sig. vs. placebo in childhood-onset group). Exercise capacity was measured in 3 trials but improvement was demonstrated in only a subset of 20 patients with childhood-onset GHD from the largest trial (Chipman 1997). Bone mineral density was improved in one trial (Snyder 2007), increasing by 2.9% in the lumbar spine of patients receiving GH treatment compared to 1.4% in the placebo group (p< 0.05). One of the most common markers clinicians use to detect the effectiveness of GH replacement because it roughly parallels GH levels and which has many of the same catabolic effects on the body as GH is the insulin-like growth factor or IGF-I. All 5 RCTs reported increases of IGF-I levels in the serum of patients receiving GH, ranging from approximately 89 to 241µg/L in 3 trials, and in the other 2 trials nearing or exceeding normalization in comparison to a reference (SD score between -0.18 and +3.2). Consistent reporting of several other surrogate markers including bone mineral content, bone metabolism markers, and cardiac structure and function was lacking. **The clinical significance of these changes is not known.**

Only 3 trials (Chipman 1997, Chihara 2005, and Snyder 2007) reported adverse events. Meta-analysis of adverse effects were done using RevMan 5.0 of eth Cochrane collaboration soft ware. Edema (2 trials, RR with 95% CI 3.6 (.2 to 10.5); peripheral edema (2 trials, RR with 95% CI: 10.4 (2.0 to 54.1) are commonly associated with GH and were significantly increased compared to patients receiving placebo. Arthralgia (2 trials, RR with 95% CI: 2.3 (0.9 to 6.1); paraesthesia (2 trials, RR with 95% CI 5.0 (0.9 to 27.9) and headache (2 trials, RR with 95% CI: 1.3 (0.6 to 3.1) did not significantly differ from placebo group.

11. CONCLUSIONS

- There is insufficient evidence that Humatrope provides a therapeutic advantage in terms of mortality, morbidity or QoL over other biosynthetic human growth hormone products or compared with placebo in the treatment of adults with adult- or childhood-onset growth hormone deficiency.

- No controlled studies establish the appropriate long-term dose of synthetic GH or the serious morbidity and mortality benefit or harm of long term GH replacement in adults.

Note: This systematic review report was not sent for external review.

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13. APPENDIX A

Summary of Results from Included Trials comparing Humatrope versus placebo

Nass R et al 1995 was a 6-month DB RCT (placebo-controlled) in 20 men and women with adult-onset GH deficiency. 75% of the patients were male. The dose of GH was fixed at 12.5µg/kg/day. The mean age of patients in the GH and placebo groups was 45 and 44 years of age, respectively. For a diagnosis of GHD, patients had to have low IGF-I levels (less than 120ng/mL), and a peak serum GH response below 2ng/mL on a GH stimulation test (ITT or arginine).

Nass et al 1995 (trial duration: 6 months)		
Source	Journal publication	
Treatment Groups & dose	**GH (12.5 µg/kg/day)**	**Placebo**
Number of patients randomized to treatment	10	10
Total Withdrawals	NR	NR
WDAEs	NR	NR
Results		
Mortality	NR	NR
Non-fatal SAEs	NR	NR
Quality of Life Scores	NR	NR
Muscle Strength	NR	NR
Exercise Capacity	Mean ± SEM N = 10	Mean ± SEM N = 10
VO_2 max (L/min)		
baseline	1.9 ± 0.2	1.9 ± 0.18
endpoint	2.6 ± 0.18**	2.2 ± 0.18
VO_2 max per kg body weight, % of expected value		
baseline	81.8 ± 10.2	84.6 ± 5.9
endpoint	110.8 ± 7.9§	98.1 ± 8.1
Maximal O_2 Pulse (mL/beat)		
baseline	15.2 ± 5.6	14.3 ± 1.2
endpoint	19.6 ± 3.3**	16.3 ± 1.1
Maximal Power Output (Watt)		
baseline	192.5 ± 13.5	187.5 ± 16.8
endpoint	227.5 ± 11.5**	192.5 ± 14.9
Maximal Power Output per kg of Body Weight (watts/kg)		
baseline	2.2 ± 0.17	2.1 ± 0.19
endpoint	2.4 ± 0.18**	2.1 ± 0.13
Maximal Power Output per kg of Lean Body Mass (watts/kg)		
baseline	3.7 ± 0.3	3.8 ± 0.2
endpoint	3.5 ± 0.3	3.8 ± 0.1
Maximal Ventilation (L/min)		
baseline	53.4 ± 6.3	50.5 ± 5.3
endpoint	59.4 ± 6.0*	53.9 ± 5.7
Anaerobic threshold per kg of Body Weight (mL/min x kg)		
baseline	16.9 ± 1.8	16.0 ± 1.0
endpoint	20.4 ± 1.7**	18.4 ± 1.2*
Exercise time (min)		
baseline	6.4 ± 0.6	6.1 ± 0.7
endpoint	6.8 ± 0.5*	6.2 ± 0.6

	*P < 0.05 vs baseline **P < 0.01 vs baseline §P < 0.005 vs. baseline *Note: statistical significance was similar for comparison of VO_2 max per kg body weight as for VO_2 max.*	*P ≤ 0.05 vs baseline
Body Composition Lean Body Mass (kg) baseline endpoint	Mean ± SEM N = 10 52 ± 1.9 56.6 ± 2.0** **P < 0.01 vs. baseline	Mean ± SEM N = 10 47 ± 3.9 49.9 ± 3.1
IGF-I (ng/mL) baseline endpoint	Mean ± SEM N = 10 62.4 ± 11.6 303.1 ± 48.9§ §P < 0.005 vs. baseline	Mean ± SEM N = 10 55.8 ± 10.4 58.8 ± 9.5
Bone Mineral Density	NR	NR
Cardiac Structure/Function	*note that all cardiac parameters measured in patients receiving GH did not change significantly (P=NS) from baseline (refer to notes section)* *Maximal systolic & diastolic blood pressure and maximal heart rate did not change (P=NS)*	*note that all cardiac parameters in patients receiving placebo did not change significantly (P=NS) from baseline (refer to notes section)* *Maximal systolic & diastolic blood pressure and maximal heart rate did not change (P=NS)*
Lipid Levels	NR	NR
Total AEs	4/10 (40%)	0 (0%)
Lab values/vital signs	NR	NR
Additional notes	The baseline patient demographics and characteristics were similar between GH and placebo groups. Measured cardiac parameters included: size in millimeters of the interventricular septum (IVS), left ventricular posterior wall (LVPW), left ventricular end-systolic dimension (LV-ESD), LV-EDD (left ventricular end-diastolic dimension), FS (fractional shortening), LVM (left ventricular mass), LA (left atrium), and LVM/body surface area.	
NR = Not Reported; NS = not statistically significant; SEM = standard error of the mean		

Chipman et al 1997 was two identical studies, each a 6 month DB RCT (placebo-controlled) in men and women differing only in age of onset: either adult- (N=98) or childhood-onset (N=67) GH deficiency. The initial dose was fixed at 6.25µg/kg/day, followed 1 month later by an increase to 12.5µg/kg/day. The mean age of patients with adult- and childhood-onset GHD was 44 and 28 years of age, respectively. Males made up 67% of all randomized patients. For a diagnosis of GHD, patients had to have a peak serum GH concentration of less than 5mg/L on a GH stimulation test (patients with childhood-onset GHD were required to be off GH therapy for at least 2 years prior to

repeated testing). Patients either switched from placebo to GH or continued on GH for a 12-month open-label phase followed by another extension of 20 months.

Chipman 1997 (trial duration: 6 months; 2 identical studies – #1 with AO patients, -#2 with CO patients). Secondary publications: Attanasio 1997 and Gullestad 1998				
Source	**Journal publication**			
	Adult-Onset (AO) GHD (Study #1)		**Childhood-Onset (CO) GHD (Study #2)**	
Treatment Groups & dose	**GH (12.5µg/kg/day)**	**Placebo**	**GH (12.5µg/kg/day)**	**Placebo**
Number of patients randomized to treatment	52	46	32	35
Total Withdrawals	3 (5.8%)	2 (4.3%)	4 (12.5%)	5 (14.3%)
WDAEs	1 (1.9%)	NR	2 (6.3%)	NR
Results				
Mortality	NR	NR	NR	NR
Non-fatal SAEs	none	none	none	none
Quality of Life Scores	NR	NR	NR	NR
Muscle Strength & Exercise Endurance	NR	NR	NR	NR
Body Composition	NR	NR	NR	NR
IGF-I (& IGFBP) Levels	NR	NR	NR	NR
Lipid Levels	NR	NR	NR	NR
Bone Mineral Density	NR	NR	NR	NR
	Mean ± SD N=52	Mean ± SD N=46	Mean ± SD N=32	Mean ± SD N=35
Fasting Glucose				
baseline	4.37 ± 0.99	4.44 ± 0.65	4.60 ± 0.68	4.57 ± 0.91
endpoint change	+0.13 ± 0.87**	-0.18 ± 0.63	+0.34 ± 0.93*	-0.09 ± 0.68
Fasting Insulin (mU/L)				
baseline	14.68 ± 8.13	18.84 ± 14.29	14.05 ± 8.44	13.43 ± 7.95
endpoint change	+3.94 ± 12.11	+3.14 ± 22.32	+6.06 ± 13.13**	-1.35 ± 10.53
Glycosylated Hemaglobin				
baseline	5.17 ± 0.59	5.14 ± 0.50	5.12 ± 0.80	4.92 ± 0.56
endpoint change	+0.18 ± 0.67	-0.03 ± 0.56	+0.10 ± 0.79	+0.15 ± 0.34
	****P < 0.01 vs. Placebo**		***P < 0.05 vs. Placebo **P < 0.01 vs. Placebo**	
Total AEs	NR	NR	NR	NR
	% of Patients (n) N = 52	% of Patients (n) N = 46	% of Patients (n) N = 32	% of Patients(n) N = 35
AE:				
edema	17.3 (9)* ARI 13% NNH 8	4.4 (2)	6.3 (2)	0 (0)
peripheral edema	11.5 (6)* ARI 12% NNH 9	0 (0)	3.1 (1)	0 (0)
arthralgia	9.6 (5)	2.2 (1)	3.1 (1)	0 (0)
myalgia	7.7 (4)	4.4 (2)	3.1 (1)	0 (0)
headache	5.8 (3)	4.4 (2)	6.3 (2)	5.7 (2)
joint disorder	5.8 (3)	0 (0)	0 (0)	0 (0)
paraesthesia	3.9 (2)	2.2 (1)	3.1 (1)	0 (0)
	***P < 0.05 vs. Placebo**			
Lab values/vital signs				
Blood Pressure (mmHg)				
systolic	no sig. changes	NR	-6.41 ± 11.72**	no sig. changes
diastolic	no sig. changes	NR	NR	NR
SGOT elevated	NR	NR	12.5% (4/32) **P < 0.01 vs. baseline	0%

Outcomes of Efficacy from secondary publication (Attanasio 1997)				
Quality of Life Score **Notthingham Health Profile (NHP) Questionnaire** (see notes)	NR Sig. improvements in all NHP subscales (Social isolation & physical mobility subscales sig. lower vs. placebo P<0.01)	NR Sig. improvements in all NHP subscales	NR Sig. improvements in all NHP subscales	NR Sig. improvements in all NHP subscales
Muscle Strength & Exercise Endurance	NR	NR	NR	NR
Body Composition Lean Body Mass (kg) baseline endpoint change Body Fat (%) baseline endpoint change Sum of skinfolds (mm) baseline endpoint change §P< 0.001 vs baseline **¥P < 0.01 vs Placebo** **‡P< 0.001 vs Placebo**	Mean ± SD N = 52 57.9 ± 14.9 +3.54 ± 8.5§‡ 29.5 ± 13.8 -4.93 ± 12.3§‡ 82.0 ± 29.6 -9.6 ± 16.2§¥	Mean ± SD N = 45 55.9 ± 14.2 -0.22 ± 5.5 34.1 ± 12.0 +0.19 ± 7.4 N = 46 93.0 ± 34.7 -3.6 ± 13.6	Mean ± SD N = 32 43.5 ± 9.5 +3.68 ± 4.1§‡ 32.2 ± 10.5 -5.50 ± 6.2§‡ N = 31 83.2 ± 39.3 -14.4 ± 17.9§† §P < 0.001 vs baseline **†P < 0.05 vs Placebo** **‡P < 0.001 vs Placebo**	Mean ± SD N = 35 43.4 ± 13.4 -1.91 ± 5.7 30.8 ± 13.0 +3.38 ± 8.2* 85.1 ± 34.9 -3.2 ± 20.2 *P < 0.05 vs. baseline
  Serum IGF-I (ng/mL) baseline endpoint change Serum IGFBP-3 (ng/mL) baseline endpoint change (note: IGF-I target range is: 140-350 ng/mL)	Mean ± SD N = 46 73.4 ± 40.1 +143.4 ± 101.4§‡ 2475 ± 993 +997 ± 953§‡ §P< 0.001 vs baseline **‡P< 0.001 vs Placebo**	Mean ± SD N = 46 70.3 ± 31.6 +2.5 ± 18.9 2317 ± 929 -33 ± 554	Mean ± SD N = 32 60.7 ± 69.5 +123.5 ± 106.8§‡ 1563 ± 1042 +1088 ± 822§‡ §P < 0.001 vs baseline **‡P < 0.001 vs Placebo**	Mean ± SD N = 34 54.4 ± 45.7 +1.1 ± 23.9 N = 35 1596 ± 970 +42 ± 408
  Total Cholesterol (mg/dL) baseline endpoint change LDL-Cholesterol (mg/dL) baseline endpoint change HDL-Cholesterol (mg/dL) baseline endpoint change **P < 0.01 vs baseline §P≤ 0.001 vs baseline **†P < 0.05 vs Placebo**	Mean ± SD N = 51 241.6 ± 56.7 -18.6 ± 44.9** 180.4 ± 61.7 -20.3 ± 49.3§ 30.5 ± 11.4 +8.9 ± 10.9§†	Mean ± SD N = 45 245.2 ± 51.7 -3.2 ± 26.8 180.8 ± 56.5 -6.0 ± 32.0 32.7 ± 10.4 +4.4 ± 7.4§ §P< 0.001 vs baseline	Mean ± SD N = 30 211.3 ± 45.1 -9.9 ± 47.1 141.4 ± 46.6 -7.1 ± 51.3 33.9 ± 12.7 +4.5 ± 12.4* *P < 0.05 vs baseline	Mean ± SD N = 32 220.5 ± 61.5 +0.6 ± 39.6 148.3 ± 53.4 -7.4 ± 57.3 39.0 ± 13.3 +3.3 ± 11.5
Bone Mineral Density	NR	NR	NR	NR
Bone Metabolism Markers				

Osteocalcin (µg/L) endpoint change	NR (sig. increase vs. baseline, P < 0.02)	NR	NR (sig. increase vs. baseline, P < 0.02)	NR
Glucose Levels	NR	NR	NR	NR
Total AEs	NR	NR	NR	NR
Additional notes	The dose of GH was stepped-up at 4 weeks from 6 to a maximum of 12.5µg/kg/day. At baseline, AO patients had statistically significantly higher mean age, height, weight, BMI, waist/hip ratio, lean body mass, body fat mass, IGF-I, and IGFBP-3 levels compared to CO patients. Osteocalcin and HDL cholesterol levels were significantly lower. Only % body fat, total skin fold length, and total cholesterol levels were similar. In terms of the NHP subscale scores at baseline, AO patients scored significantly higher on "physical mobility", and "energy level" compared to CO patients, while the "social isolation", "emotional reaction", "sleep" and "pain" subscales were similar amongst the 2 groups. The majority of patients (16) with adult-onset GHD experienced AEs during the first 3 months of receiving GH; during the last month of therapy only 2 patients reported AEs. In a subgroup analysis of patients reporting at least 1 AE vs. those without an AE, the ones with AEs were heavier, had a significantly higher body-mass index at baseline, and received more of the GH product. However, 3 months into the trial change in lean body mass, % body fat, and HDL cholesterol was not significantly different between the 2 groups. IGF-I levels increased significantly in the group of patients with 1 or more AEs. This trial examined only the safety profile of GH-treated patients; quality of life, body composition, exercise endurance and muscle strength were not reported. Patients over 60 years of age were not included in the trial. The NHP, a quality of life questionnaire, is composed of 6 subscales: "social isolation", "physical mobility", "emotional reaction", "energy level", "sleep", and "pain". A higher score indicates better quality of life. Patients with GHD were selected then placed into 2 protocols based on their onset of GHD (Adult-onset or childhood-onset) not using a randomization procedure. This led to several statistically significant differences between the 2 groups in terms of their baseline demographics and characteristics. The heterogeneity may have affected how the results from the 2 groups could be compared. For the surrogate outcomes (except for the NHP scale) P-values were given for comparisons between GH and Placebo, but not for AO vs. CO groups.			

AO = adult-onset GHD; ARI = absolute risk increase; CO = childhood-onset GHD; NNH = number needed to harm; NHP = Nottingham Health Profile; NR = Not Reported; NS = not statistically significant; ; PLC = placebo; SD = standard deviation; SE = standard error of the mean ; SGOT = aspartate transaminase; Sig. = statistically significant

Chipman 1997 (AEs from 12 month Open-Label Phase [month 6-18]) – all patients in this phase received GH

	GH-treated patients (AO) – Study #1 N (% of Patients)	**GH-treated patients (CO) – Study #2** N (% of Patients)
AEs:	N = 44	N = 30
edema	5(11.4)	3(10)
peripheral edema	8(18.2)	1(3.3)
arthralgia	6(13.6)* **ARI 13.6% NNH =7**	0 (0)
myalgia	4(9.1)	2(6.7)
headache	3(6.8)	2(6.7)

joint disorder paraesthesia	1(2.3) 6(13.6)* **ARI 13.6% NNH =7** **P < 0.05 vs. Placebo**	0 (0) 0 (0)
Notes	Reporting for 12 month open-label phase following the 6 month DB RCT is shown below: 14 (14%) adult-onset and 19 (28%) childhood-onset GHD patients withdrew from the study after 12 additional months of open-label therapy with GH; during this period 12 AO patients had SAEs (3 SAEs occurred in CO patients, but the number of patients w/SAEs was not given). Hypertension was reported in 7.7% of AO patients treated with GH; no CO patients had hypertension. There were no statistically significant changes in fasting glucose, insulin, or glycosylated hemoglobin for AO and CO patients during the 12-month open-label phase of the trial. **Reporting of the additional open-label 20 month extension phase is shown below:** In the ongoing extension phase following 12 months of open-label therapy with GH, the interim results showed no deaths, and 10 versus 1 SAEs in AO and CO patients, respectively. During this period, 6 AO patients had systolic blood pressure > 150 mm Hg, and 10 had diastolic BP > 90 mm Hg. Abnormal diastolic BP appeared in 2 CO patients.	
AO = adult-onset GHD; ARI = absolute risk increase; CO = childhood-onset GHD; NNH = number needed to harm		

Fernholm et al 2000 was a 6-month, multicentre DB RCT (placebo-controlled) in elderly men and women (N = 31) with adult-onset GH deficiency. The majority (81%) of patients were male; mean age was 68 years old. For the initial month, the dose of GH was fixed at 0.05 IU/kg/week then increased to 0.1 IU/kg/week for the next 5 months of therapy. GH-treated patients received a mean GH dose of 0.92 ± 0.2 IU/day (range: 0.75-1.25). For a diagnosis of GHD, patients had to have a peak serum GH concentration of less than 3µg/L using a GH stimulation test (ITT or arginine).

Fernholm 2000 (trial duration: 6 months DB; elderly patients 60-79 years old) Secondary publication: Elgzyri 2004		
Source	Journal publication	
Treatment Groups & dose	**GH (0.033 mg/kg/week)**	**Placebo**
Number of patients randomized to treatment	15	16
Total Withdrawals	none	none
WDAEs	none	none
Results		
Mortality	none	none
Non-fatal SAEs	NR	NR
Quality of Life Scores	NR	NR
Muscle Strength	NR	NR
Body Composition Lean Body Mass (kg) baseline endpoint Total Body Fat (kg) baseline endpoint	Mean ± SEM N = 15 52.1 ± 1.6 54.5 ± 2.1* 22.3 ± 1.8 20.7 ± 1.6* ***P < 0.05 vs. Placebo**	Mean ± SEM N = 16 46.6 ± 2.7 46.9 ± 2.8 24.1 ± 1.1 24.1 ± 1.2

IGF-I (µg/L) baseline endpoint IGFBP-3 (µg/L) baseline endpoint (reference values for IGF in healthy subjects are shown in the notes section)	Mean ± SEM N = 15 55.8 ± 5.2 145 ± 14† 1218 ± 103 1914 ± 156† †**P < 0.001 vs. baseline & vs. Placebo** *Note that IGF-II and IGFBP-4,5 levels (not shown here) were statistically significantly increased at the 6 month study endpoint compared to both baseline and placebo; whereas IGFBP-1,2 levels were significantly decreased compared to baseline and placebo.*	Mean ± SEM N = 16 70.4 ± 9.0 70.0 ± 8.9 1607 ± 184 1562 ± 174 *Note that for all the IGF and IGFBP surrogate markers measured in patients receiving the placebo, there were no statistically significant differences at the 6-month endpoint compared to baseline.*
Bone Mineral Density	BMD in the lumbar spine, femoral neck, trochanter regions and in the total body did not change during treatment.	
Bone Metabolism Markers: Osteocalcin (µg/L) baseline endpoint PICP (µg/L) baseline endpoint ALP (µg/L) baseline endpoint U-Pyridinoline (µg/L) baseline endpoint (Reference values for bone markers in healthy subjects are shown in the notes section)	Mean ± SEM N = 15 18 ± 1.3 32.2 ± 2.1†‡ 76 ± 6.4 118 ± 9.6†‡ 8.8 ± 0.7 11.6 ± 1.1†‡ 422 ± 42 633 ± 98*§ *P < 0.05 vs. baseline †P < 0.001 vs. baseline **§P = 0.01 vs. Placebo** **‡P ≤ 0.001 vs. Placebo**	Mean ± SEM N = 16 20.5 ± 2.0 20 ± 1.7 80.9 ± 6.6 79.8 ± 6.8 10 ± 1.2 9.3 ± 1.2 473 ± 101 384 ± 56
Insulin (pmol/L) baseline endpoint	Mean ± SEM N = 15 48.8 ± 6.4 69.6 ± 9.3* ***P < 0.05 vs. baseline & vs. Placebo**	Mean ± SEM N = 16 63.1 ± 7.9 59.6 ± 8.6
Outcomes of Efficacy from Secondary Publication (Elgzyri 2004):		
Cardiac Function Heart rate at rest (bpm) baseline endpoint Heart rate at max exercise baseline endpoint	Median (range) N = 15 58 (48-75) 67 (50-86)* 142 (102-162) 148 (107-160)*	Median (range) N = 16 70 (47-102) 66 (45-110) 147 (112-179) 138 (113-177)

Exercise Capacity Max work load (watts) baseline endpoint	150 (105-180) 160 (110-210)* *P ≤ 0.05 vs. baseline *Note that all other cardiac parameters measured in patients receiving GH did not change significantly (P=NS) from baseline (refer to notes section)*	129 (70-210) 140 (80-120) *Nnote that all cardiac parameters (including those listed above) in patients receiving placebo did not change significantly (P=NS) from baseline (refer to notes section)*
Lipid Levels Total Cholesterol (mmol/L) baseline endpoint LDL Cholesterol (mmol/L) baseline endpoint HDL Cholesterol baseline endpoint LDL/HDL ratio baseline endpoint Trigylcerides baseline endpoint	Mean N = 15 5.7 5.2* 3.9 3.3* NR NR 3.7 3.0* NR NR *P < 0.05 vs. baseline	Mean N = 16 5.8 5.5* 4.0 3.6* NR NR 3.8 3.1** NR NR *P < 0.05 vs. baseline **P < 0.01 vs. baseline
Total AEs	NR	NR 1 patient with an unspecified side-effect
Lab values/vital signs Blood Pressure systolic diastolic	 NR NR	 NR NR
Notes	The starting dose of GH was 0.017 mg/kg/week given for the first month, and then increased to 0.033 mg/kg/week. The mean GH dose received by patients during the study was 0.3 ± 0.07 mg/day. There was no difference between treatment groups in the age, body mass index, or etiology of hypo pituitarism of patients at baseline, and all patients had IGF-I levels below normal for mean age. The normal range for the following surrogate markers in healthy subjects is: IGF-I in 20 (159-481µg/L), 65 (78-235µg/L), and 75 (66-200µg/L) year olds. The mean IGFBP-3 in 50-70 year olds is 2966 ± 439µg/L. The reference for osteocalcin is <30µg/L in men and <50µg/L in postmenopausal women. The PICP range is 40-200µg/L in men and 50-170µg/L in women. The mean ALP is 12.3 ± 4.3µg/L in men and 11.5 ± 4.3µg/L in women. The measured cardiac parameters were: aorta outflow tract integral (VTI), AV-plane movement, fractional shortening, diastolic closing motion of the mitral valve leaflets (EF slope), rapid filling wave (E wave), rapid filling wave/atrial filling wave (E/A ratio), pulmonary vein systolic/diastolic wave (S/D ratio), left ventricular interior diameter at diastole and systole (LVIDd	

	& LVIDs), posterior wall dimension, septum dimension, left arterial dimension, heart rate at rest, heart rate at max exercise, and max work load. Efficacy outcomes from the 12 month open-label phase following the 6 month DB RCT are not addressed in this review. The study authors did not provide any data on safety, except that three patients withdrew from the open-label phase. The majority (81%) of patients were male; 22 of them were receiving testosterone replacement. Patients were mostly the elderly.
ALP = bone-specific alkaline phosphatase; BMD = Bone Mineral Density; NR = Not Reported; NS = not statistically significant; PICP = carboxyl-terminal propeptide of type I procollagen; SD = standard deviation; SEM = standard error of the mean	

Chihara K et al 2004 was a 24-week, multicentre DB RCT (placebo-controlled) in men and women (N = 64) with childhood (N=37) and adult-onset (N=27) GH deficiency. Patients were stratified according to onset of GHD. Males represented 48% of all randomized patients. The initial dose was fixed at 3µg/kg/day, subsequently increased to 6 then 12µg/kg/day. At the end of the 24 weeks of the study the GH-treated patients received a mean GH dose of 0.078 ± 0.015 mg/kg/week (range: 0.021-0.085). The mean age of patients with adult and childhood-onset GHD was 51 and 29 years of age, respectively. For a diagnosis of GHD, patients had to have a peak serum GH concentration of less than 3µg/L on a GH stimulation test (ITT, arginine or glucagon).

Chihara 2004 (trial duration: 24 weeks; patients: Japanese men and women) Secondary publications: Chihara 2005 and Urushihara 2007				
Source	Journal publication			
	Adult-Onset (AO) GHD		**Childhood-Onset (CO) GHD**	
Treatment Groups & dose	**GH (12.0µg/kg/day)**	**Placebo**	**GH (12.0µg/kg/day)**	**Placebo**
Number of patients randomized to treatment	14	13	19	18
Total Withdrawals (from Urushihara 2007)	2 (14%)	2 (15%)	0	1 (5.6%)
WDAEs	NR	NR	NR	NR
Results				
Mortality	NR	NR	NR	NR
Non-fatal SAEs	NR	NR	NR	NR
Quality of Life Score **Short Form-36 v.2 Health Survey (from Urushihara 2007) Subscales:**	Mean ± SD endpoint change **For all SF-36 subscales in AO patients, P=NS vs. Placebo**	Mean ± SD endpoint change	Mean ± SD endpoint change	Mean ± SD endpoint change
mental health	NR*	NR*	+2.6 ± 12.4*‡	-7.8 ± 17.7*
bodily pain	-12.8 ± 20.6**	NR*	NR*	NR*
physical functioning	NR*	NR*	NR*	NR*
role physical	NR*	NR*	NR*	NR*
general health	NR*	NR*	NR*	NR*
vitality	NR*	NR*	NR*	NR*
social functioning	NR*	NR*	NR*	NR*
role emotional	*P = NS vs. baseline **P=0.044 vs baseline	*P=NS vs. baseline	*P = NS vs. baseline ‡**P=0.045 vs. Placebo**	*P = NS vs. baseline
Muscle Strength &	NR	NR	NR	NR

Exercise Endurance				
Body Composition Lean Body Mass baseline (kg) endpoint change (kg)† % change Fat Mass baseline (kg) endpoint change (kg)† % change † = imputed value	Mean ± SD (n=13) 39.4 ± 10.0 +2.17 +5.5 ± 3.2* 21.5 ± 7.4 -1.55 -7.2 ± 7.1** ***P < 0.001 vs PLC** ****P = 0.005 vs PLC**	Mean ± SD (n=12) 36.9 ± 8.3 -0.74 -2.0 ± 3.8 20.9 ± 6.0 +0.46 +2.2 ± 8.1	Mean ± SD (n=19) 41.4 ± 9.7 +1.74 +4.2 ± 4.3* 22.9 ± 8.0 -2.40 -10.5 ± 14.2** ***P = 0.014 vs PLC** ****P = 0.006 vs PLC**	Mean ± SD (n=17) 40.5 ± 11.3 +0.24 +0.6 ± 4.1 19.1 ± 7.7 +0.08 +0.4 ± 6.0
  IGF-I (µg/L) baseline endpoint change IGF-I SD Score baseline endpoint change† IGFBP-3 (mg/L) baseline endpoint change IGFBP-3 SD Score baseline endpoint change† † = means and SD combined from male & female groups (calculated)	Mean ± SD (n=14) 89 ± 54 NR -1.12 ± 1.15 +3.25 ± 2.00** 2.5 ± 1.1 ND -1.84 ± 2.83 2.40 ± 1.66** ****P < 0.00001 vs. Placebo** (P-value calculated)	Mean ± SD (n=13) 95 ± 47 NR -0.73 ± 0.93 -0.45 ± 0.73 2.5 ± 1.0 ND -1.58 ± 2.73 -0.21 ± 1.06	Mean ± SD (n=19) 48 ± 30 NR -3.37 ± 1.69 +3.23 ± 1.85** 1.6 ± 0.7 ND -5.15 ± 3.16 4.27 ± 2.78** ****P < 0.00001 vs. Placebo** (P-values calculated)	Mean ± SD (n=18) 58 ± 45 NR -2.98 ± 1.24 0.01 ± 0.49* 1.7 ± 0.9 ND -4.52 ± 3.21 -0.38 ± 1.69*
  Total Cholesterol (mg/dL) baseline† endpoint change† LDL-Cholesterol (mg/dL) baseline† endpoint change† † = mean and SD combined from male & female groups (calculated)	Mean ± SD (n=14) 227 ± 39 -26.7 ± 25.8* 135 ± 44.9 -19.3 ± 20.2* ***P≤ 0.01 vs. Placebo** (P-value calculated)	Mean ± SD (n=13) 227 ± 34.3 +2.33 ± 34.2 141 ± 40.4 +7.33 ± 30.1	Mean ± SD (n=19) 216.1 ± 48.2 -4.9 ± 37.4 122.7 ± 34.6 +2.1 ± 29.2	Mean ± SD (n=18) 195.3 ± 38.0 +11.4 ± 44.6 109.1 ± 36.3 +9.4 ± 27.2
HDL Cholesterol endpoint change Triglycerides endpoint change	P = NS‡ P = NS‡ **‡vs baseline & vs Placebo**	ND ND	P = NS‡ P = NS‡ **‡vs baseline & vs Placebo**	ND ND
Bone Mineral Density	NR	NR	NR	NR
Glucose Levels	NR	NR	NR	NR
Total AEs	NR	NR	NR	NR
AEs	**Refer to Chihara 2005 publication for the table of AEs (below)**			
Lab values/vital signs Thyroxine (T_4) **(see notes section)** Blood Pressure systolic diastolic	NR no clinical changes no clinical changes	NR no clinical changes no clinical changes	NR no clinical changes no clinical changes	NR no clinical changes no clinical changes

Additional Notes	The dose of GH was stepped-up at 4 and 12 weeks (to 6.0 and 12.0µg/kg/day) from a starting dose of 3µg/kg/day then reduced by 25-50% if side effects due to treatment began to emerge. At the end of the 24 weeks of the study the GH-treated patients received a mean GH dose of 0.078 ± 0.015 mg/kg/week (range: 0.021-0.085). AO patients were older and had a longer history of GHD than CO patients at baseline; whereas CO patients had significantly lower IGF-I and IGFBP-3 levels and SD scores. Both groups of patients were similar in terms of height SD scores, body composition, serum total cholesterol, and LDL cholesterol at baseline. Data for the total number of patients withdrawing from the study were taken from a secondary publication, Urushihara 2007. When patients from AO and CO groups were combined, those receiving GH had a statistically significant increase in lean body mass of 4.7 ± 3.9% compared to a decrease of -0.5 ± 4.1% in the placebo group (P < 0.001). Fat mass decreased by 9.2 ± 11.8% in the GH group and increased by 1.1 ± 6.9% in the placebo group (P < 0.001). Patients receiving GH (AO+CO patients combined) also showed a significant increase in IGF-I levels from 65 ± 46 µg/L at baseline to 240 ± 115µg/dL at endpoint (P < 0.001); the placebo group showed a decrease of 8 ± 25µg/dL. Serum total cholesterol and LDL cholesterol decreased significantly by 14 ± 34mg/dL and 7 ± 27mg/dL, respectively in patients receiving GH compared to an increase of 7 ± 39mg/dL and 9 ± 27mg/dL in the placebo group (P = 0.04). Normal ranges for total- and LDL-cholesterol are: 150-219mg/dL and 70-139mg/dL, respectively. Edema rates were similar in the GH and placebo groups, respectively (12.1% and 6.5% of patients, P = NS) – refer to table of AEs below (Chihara 2005). Thyroxine (T_4) levels decreased significantly in the GH group from baseline (P < 0.001), but was NS compared to placebo. Glycosylated haemoglobin increased significantly in patients receiving GH compared to placebo (P = 0.02). The prevalence of obesity in the Japanese is lower than in Caucasians, indicating their cardiovascular health may also be different. The sample size may have been too small to detect differences in results of the surrogate markers. Some of the outcome data were combined from patients with AO and CO GHD.
AO = adult-onset GHD; CO = childhood-onset GHD; NR = Not Reported; NS = not statistically significant; PLC = placebo; SD = standard deviation; SE = standard error of the mean	

Chihara 2005 (AE data from patients in the Chihara 2004 trial, above) – AO & CO groups are combined

	GH-treated patients (AO + CO) N(% of Patients) N = 33	**Placebo (AO + CO)** N(% of Patients) N = 31
Most frequent AEs, ≥ 10% for any treatment group: (MedDRA classification)		
nasopharyngitis	11(33.3)	17(54.8)
cough	7(21.2)	6(19.4)
rhinorrhea	7(21.2)	6(19.4)
pharyngolaryngeal pain	6(18.2)	5(16.1)
upper respiratory tract inflammation	5(15.2)	4(12.9)
pyrexia	7(21.2)	12(38.7)
edema	4(12.1	2(6.5)
fatigue	1(3)	3(9.7)
arthralgia	6(18.2)	4(12.9)
back pain	2(6.1)	0 (0)
headache	6(18.2)	4(12.9)
dizziness	1(3)	0 (0)
pruritus	1(3)	4(12.9)

nausea	3(9.1)	5(16.1)
diarrhea (NOS)	2(6.1)	5(16.1)
anorexia	1(3)	5(16.1)
sputum increased	1(3)	1(3.2)

Chihara 2005 (AEs in patients after 48 weeks of Open Label GH extension)– AO & CO groups are combined		
	GH-treated patients	**Patients switched from Placebo to GH**
Most frequent AEs, ≥ 10% for any treatment group: (MedDRA classification)	N (% of Patients) N = 30	N (% of Patients) N = 28
nasopharyngitis	14(46.7)	7(25)
cough	2(6.7)	3(10.7)
rhinorrhea	4(13.3)	2(7.1)
pharyngolaryngeal pain	2(6.7)	2(7.1)
upper respiratory tract inflammation	2(6.7)	2(7.1)
pyrexia	7(23.3)	7(25)
edema	0 (0)	1(3.6)
fatigue	0 (0)	0 (0)
arthralgia	6(20)	1(3.6)
back pain	4(13.3)	2(7.1)
headache	4(13.3)	3(10.7)
dizziness	4(13.3)	1(3.6)
pruritus	0 (0)	1(3.6)
nausea	2(6.7)	0 (0)
diarrhea (NOS)	1(3.3)	2(7.1)
anorexia	1(3.3)	0 (0)
sputum increased	3(10)	2(7.1)
Notes	All patients in the open-label extension phase of the trial were given a GH dose based on the previous visit's serum IGF-I level (dose range of GH was 0.021 to 0.084 mg/kg/week). Three SAEs were reported during the open-label extension phase, however they occurred early on (before week 24). Authors stated, "no changes from baseline in laboratory parameters or systolic and diastolic blood pressures indicated any safety problems." After 48 weeks, TSH, T3, and T4 levels did not change significantly from baseline in the patients switched from placebo to GH.	
NOS = not otherwise specified		

Snyder et al 2007 was a 24-month DB RCT (placebo-controlled) in 67 men and women with adult-onset GH deficiency. The mean age of patients was 50 years old and 60% were male. The initial dose of GH was fixed at 2µg/kg/day then increased to 4 then 8µg/kg/day at the first and third months, respectively, followed by a final maximum dose of 12µg/kg/day at 6 months of therapy. The mean final dose of GH in men and women was 0.41 ± 0.26 and 0.65 ± 0.22 mg/day. For a diagnosis of GHD, patients had to have a peak serum GH response below 2.4µg/L on a GH stimulation test (ITT or arginine/L-Dopa).

Snyder 2007 (trial duration: 24 months DB)		
Source	Journal publication	
Treatment Groups & dose	**GH (12µg/kg/day)**	**Placebo**
Number of patients randomized to treatment (men/women)	33 (20/13)	34 (20/14)
Total Withdrawals	9 (27%)	4 (12%)
WDAEs	4 (12%)	2 (5.9%)
Results		
Mortality	none	none

Non-fatal SAEs	2 neoplasms (no. of patients not reported) + 2 patients with complications from diabetes mellitus		5 neoplasms (no. of patients not reported)	
Quality of Life Scores	NR		NR	
Exercise Endurance & Muscle Strength	NR		NR	
Body Composition Lean Body Mass (kg) baseline endpoint Trunk Fat Mass (kg) baseline endpoint	Mean ± SD N = 33 NR NR (P = NS vs. baseline) NR -1.0 ± 0.38 kg* *P < 0.03 vs. Placebo		Mean ± SD N = 34 NR NR (P = NS vs. baseline) NR NR	
IGF-I SD Score baseline† endpoint (24 months) (SD score = number of SDs from an age-adjusted mean) † baseline IGF-I SD score was available only from men & women groups combined	Men Mean ± SD N = 20 -1.65 ± 0.92† +0.48 ± 1.47	Women Mean ± SD N = 13 -1.65 ± 0.92† -0.18 ± 1.14	Men Mean ± SD (SE) N = 20 -1.91 ± 0.75† -2.02 ± 0.76 (0.17)‡ ‡mean ± SD imputed from graph (SE was converted to SD using the formula: SD = SE x √N)	Women Mean ± SD (SE) N = 14 -1.91 ± 0.75† -2.32 ± 0.60 (0.16)‡ ‡mean ± SD imputed from graph
Bone Mineral Density (g/cm^2) Lumbar Spine baseline endpoint % increase Total Hip baseline endpoint Femoral Neck baseline endpoint Trochanter baseline endpoint Intertrochanter baseline endpoint	Mean ± SD N = 33 1.05 ± 0.13 1.08 ± 0.14*§ 2.86 ± 4.94*§ 0.98 ± 0.14 1.01 ± 0.15* 0.82 ± 0.13 0.83 ± 013 0.76 ± 0.12 0.78 ± 0.13* 1.15 ± 0.16 1.18 ± 0.17* *P < 0.05 vs. baseline **§P < 0.05 vs. Placebo**		Mean ± SD N = 34 1.03 ± 0.14 1.05 ± 0.12 1.41 ± 4.37 0.95 ± 0.10 0.97 ± 0.11* 0.79 ± 0.11 0.81 ± 0.11* 0.74 ± 0.11 0.76 ± 0.12* 1.11 ± 0.12 1.12 ± 0.12 *P < 0.05 vs. baseline	
Bone Mineral Content	NR		NR	
Bone Metabolism Markers: BSALP (µg/L) baseline endpoint N-Telopeptide/creatinine baseline endpoint	Mean ± SD N = 33 9.37 ± 3.62‡ 13.31 ± 5.92‡† 25 ± 9.25‡ 41.29 ± 32.4‡**		Mean ± SD N = 34 10.29 ± 2.97‡ 11.89 ± 4.66‡* 22.74 ± 11.25‡ 28.06 ± 11.25‡	

	‡mean ± SD imputed from graph (SE was converted to SD using the formula: SD = SE x √N) **P < 0.01 vs. baseline †P ≤ 0.001 vs. baseline	‡mean ± SD imputed from graph (SE was converted to SD using the formula: SD = SE x √N) *P < 0.05 vs. baseline
Subgroup Analyses: BMD (low vs. high) BMD (women on oral vs. transdermal estrogen)	 GH-treated patients from the low BMD group had an increased spine BMD at month 18 only (P=0.005) with no significant increases seen at endpoint (P=NS). Patients from the high BMD group had increases in BMD at endpoint only (P=0.001). P=NS, oral vs. transdermal estrogen	 Patients with a low BMD at baseline who were given the placebo had significant increases (P≤0.05) in spine BMD at months 12, 18, and 24 (endpoint). BMD did not increase significantly in the high BMD group. Women on transdermal estrogen had significant increases in spine BMD at months 6, 12, 18, and 24 (P≤0.03); BMD did not increase for those on oral estrogen however.
Total AEs	NR	NR
Treatment-Emergent AEs (only 2 AEs significantly more frequent in the GH group are given): peripheral edema paraesthesias	% of Patients (n) N = 33 24.2 (8)* ARI 21% NNH 5 12.1 (4) ***P < 0.05 vs. Placebo**	% of Patients (n) N = 34 2.9 (1) 0 (0)
Lab values/vital signs % of Patients with low free thyroxine levels	21.2%	23.5%
Additional notes	The majority (60%) of patients were male. The starting dose of GH was 2µg/kg/day, which was increased to 4 then 8µg/kg/day at the first and third months, respectively, followed by a final maximum dose of 12µg/kg/day at 6 months of therapy. Further dosage adjustments were made according to a target range for serum IGF-I levels measured at regular visits, and decreased if treatment-related adverse events occurred. The mean final dose of GH in men and women was 0.41 ± 0.26 and 0.65 ± 0.22mg/day. Patients were given calcium and/or vitamin-D supplements if they were deficient in either element/vitamin. GH and Placebo groups were similar in terms of age, sex, BMD T-scores, serum IGF-I levels, causes of GHD, and number of other pituitary hormone deficiencies at baseline; body mass index was significantly higher in patients receiving the placebo (P < 0.05 vs. GH).	

BSALP = bone-specific alkaline phosphatase; BMD = Bone Mineral Density; IGF-I = insulin-like growth factor; NR = Not Reported; NS = not statistically significant; SD = standard deviation; SE or SEM = standard error of the mean.

14. APPENDIX B - Additional adverse event data

Shalet et al 2003 was a 2-year, multicentre, randomized open-label study in men and women with childhood-onset GH deficiency (N=117). The control group consisted of patients with untreated GHD (N=32). The majority (63-67%) were male; mean age was 19 years old. Patients in the GH treatment groups received either a pediatric (25µg/kg/day) or adult (12.5µg/kg/day) dose. After 2 years of therapy, the mean pediatric and adult doses were 23.7 ± 3.9 and 11.3 ± 1.9µg/kg/day, respectively. A diagnosis of GHD was reconfirmed by a peak serum GH concentration of less than 5µg/L using a GH stimulation test (ITT, arginine, glucagon, or arginine/L-dopa).

Shalet 2003 (trial duration: 2 year Randomized, Open-Label Prospective Study)			
Source	Journal publication		
Treatment Groups & dose	**GH (12.5µg/kg/day-adult)**	**GH (25µg/kg/day-pediatric)**	**No GH (Control Group)**
Number of patients randomized to treatment	58	59	32
Total Withdrawals	11 (19%)	13 (22%)	2 (6.3%)
WDAEs	NR	NR	NR
Results			
Mortality	NR	NR	NR
Non-fatal SAEs	2 patients (4 other patients with SAEs are unaccounted for-tx group NR)	NR	1 patient (4 other patients with SAEs are unaccounted for-tx group was NR)
Total AEs	NR	NR	NR
Notes	The mean GH dose received by patients in the adult and pediatric dose groups was 11.3 ± 1.9, and 23.7 ± 3.9µg/kg/day, respectively.		
NR = Not Reported			

Eli-Lilly Study (CT Registry ID #6018) was a 40 month, multicentre, non-controlled study in adults with adult- or childhood-onset GH deficiency (N=51). The mean age of patients was 38 years old and the majority (53%) were female. All patients received between 0.021 and 0.084 mg/kg/week of GH. After 40 months, the mean dose range of GH was 0.048 to 0.050 mg/kg/week.

Eli-Lilly Clinical Trial (study B9R-JE-K03A, ID #6018; trial duration: 40 month, Non-Controlled)	
Source	Journal publication
Treatment Groups & dose	**GH**
Number of patients randomized to treatment	51
Total Withdrawals	15
WDAEs	2 (3.9%)
Results	
Mortality	none
Non-fatal SAEs	6 (11.8%)
Total AEs	50 (98%)
Treatment-Emergent AEs (most frequent AEs in ≥ 5% patients) MedDRA classification:	N(% of Patients) N = 51
tinnitus	3(5.9)
eye pruritus	5(9.8)

conjunctivitis allergic	4(7.8)
diarrhea, NOS	15(29.4)
nausea	10(19.6)
abdominal pain,upper	8(15.7)
vomiting, NOS	8(15.7)
gastroenteritis, NOS	7(13.7)
abdominal pain, NOS	6(11.8)
gastritis, NOS	5(9.8)
toothache	4(7.8)
gingivitis	3(5.9)
constipation	3(5.9)
stomatitis	3(5.9)
pyrexia	20(39.2)
malaise	8(15.7)
fall	5(9.8)
rigors	4(7.8)
fatigue	3(5.9)
seasonal allergy	9(17.6)
tooth caries, NOS	5(9.8)
tinea pedis	3(5.9)
sputum increased	5(9.8)
anorexia	6(11.8)
arthralgias	13(25.5)
back pain	12(23.5)
muscle stiffness	6(11.8)
pain in limb	4(7.8)
myalgia	3(5.9)
headache	15(29.4)
hypoesthesia	5(9.8)
depressed consciousness	3(5.9)
insomnia	4(7.8)
nasopharyngitis	36(70.6)
cough	19(37.3)
rhinorrhea	15(29.4)
pharyngolaryngeal pain	13(25.5)
rhinitis allergic, NOS	11(21.6)
sneezing	7(13.7)
upper respiratory tract infection	6(11.8)
bronchitis, NOS	4(7.8)
nasal congestion	4(7.8)
epistaxis	3(5.9)
rhinitis, NOS	3(5.9)
eczema	6(11.8)
rash, NOS	5(9.8)
contusion	4(7.8)
pruritus	3(5.9)
swelling (face)	3(5.9)
urticaria, NOS	3(5.9)
dental treatment, NOS	3(5.9)
Notes	The mean GH dose received by patients in the adult and pediatric dose groups was 11.3 ± 1.9, and 23.7 ± 3.9µg/kg/day, respectively.

NOS = not otherwise specified

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Somatropin (Omnitrope®)
Sandoz Canada Inc.

Description:

Drug review of somatropin (Omnitrope®), a subsequent entry biologic (SEB), for the following Health Canada approved indication:

> 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.

In their review, the DBC also considered the review completed by the Common Drug Review (CDR) in December, 2009, which included evidence review material and the recommendation from the Canadian Expert Drug Advisory Committee (CEDAC).

Dosage Forms:

5 mg/1.5 mL solution for injection cartridge
10 mg/1.5 mL solution for injection cartridge

Recommendation:

The Drug Benefit Council (DBC) recommends that somatropin (Omnitrope®) be listed similar to other growth hormones which are listed as Limited Coverage drugs with the following criteria:

> *For children 20 years of age and under, when prescribed by an endocrinologist at the British Columbia Children's Hospital for true growth hormone deficiency or chronic renal insufficiency.*

The DBC also recommends that the Ministry explore a coverage policy that may take advantage of the product's lower cost compared to other covered growth hormone products.

Reasons for the Recommendation:

1. **The clinical efficacy and safety of Omnitrope and comparator product Genotropin appear similar**
   - A literature review identified one open-label randomized controlled trial (RCT) comparing Omnitrope to Genotropin in children with growth hormone deficiency. Genotropin, approved though not marketed in Canada, is considered the reference standard for somatopin products.
   - Based on this trial, the clinical efficacy of Omnitrope appears similar to Genotropin.
   - There is no evidence available to support use of Omnitrope in adults with growth hormone deficiency.
   - There are no apparent safety differences between Omnitrope and Genotropin.
   - While there is a possible higher rate of induction of anti-growth hormone antibodies and anti-HCP antibodies with Omnitrope compared to Genotropin, this difference is of unknown clinical significance.

2. **Economic Considerations**
   - The cost of Omnitrope is lower than cost of other growth hormones currently covered by PharmaCare. This comparison is based upon product list costs and product dosing as outlined in the product monograph.

3. **The clinical efficacy and safety of Omnitrope are expected to be similar to other growth hormone products covered by BC PharmaCare**
   - The available somatropin products exert similar pharmacologic effects to mimic growth hormone but have different bio-production processes.
   - While no clinical or pharmacokinetic data was reviewed comparing Omnitrope and other growth hormone products covered by PharmaCare, there is no reason to expect significant clinical differences between products.
   - Because the clinical profile of Omnitrope is expected to be similar to other growth hormone products and the cost of Omnitrope is lower, the Ministry should explore coverage policy options which may lower the overall budget impact of growth hormone product coverage.