Common Drug Review
Clinical Review Report

January 2014

Drug	somatropin (Genotropin) for subcutaneous injection
Indication	Long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone
Listing request	List in a similar manner to other growth hormone products
Manufacturer	Pfizer Canada Inc.

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CDR	Common Drug Review
GH	growth hormone
GHD	growth hormone deficiency
HtSDS	height standard deviation score
HV	height velocity
HVSDS	height velocity standard deviation score
IGF-1	insulin-like growth factor-1
ITT	intention-to-treat population
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SDS	standard deviation score
SMR	standardized mortality ratio

EXECUTIVE SUMMARY

Introduction

Growth hormone deficiency (GHD) is the most common endocrine cause of short stature, although growth failure is also associated with other causes, such as Turner syndrome, Prader-Willi syndrome, and chronic renal insufficiencies. Diagnosis of GHD is usually based on a combination of auxologic assessment, biochemical tests (growth hormone stimulation tests) and neuroimaging of the hypothalamic-pituitary region. The prevalence of GHD is estimated to be between 1 in 3,500 and 1 in 4,000 children. Once the diagnosis of GHD is established in children, recombinant human growth hormone (also called somatropin) therapy is recommended as soon as possible in order to enhance growth velocity and normalize final adult height.

Genotropin is one of several somatropin products available in Canada and is indicated for treatment of pediatric GHD at a dose of 0.16 mg/kg to 0.24 mg/kg body weight per week divided into six to seven doses and administered by subcutaneous injection. According to the product monograph, the dose of Genotropin should be adjusted based on the concentration of insulin-like growth factor-1 and adverse effects.

The objective of this systematic review is to compare the benefits and harms of Genotropin with other available somatropin products in children with GHD.

Indication under review
Long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone
Listing criteria requested by sponsor
List in a similar manner to other growth hormone products

Results and Interpretation

Included Studies

Two parallel randomized controlled trials of children with GHD were included in this review. One phase 3 open-label trial (Romer et al., n = 89, nine months' duration) was conducted in Europe and compared Genotropin 0.03 mg/kg per day (subcutaneously) with Omnitrope 0.03 mg/kg per day (subcutaneously). Shih et al. (n = 15, 12 months' duration) was conducted in Taiwan and compared Genotropin 0.1 IU/kg per day with Humatrope 0.1 IU/kg per day and Saizen 0.2 IU/kg three times a week. Romer et al. was designed as an equivalence study and had a pre-set equivalence margin of 2 cm per year for height velocity. The primary outcomes in the two trials were all height-related (Romer et al.: height, height standard deviation score [HtSDS], height velocity [HV], and height velocity standard deviation score [HVSDS]; Shih et al.: height, HV, and HtSDS) at study end.

Efficacy

In the two included trials, the mean increase in height from baseline to the study end (ninth month or twelfth month) in children with GHD ranged from 8 cm to 11 cm across the somatropin products (Genotropin, Omnitrope, Humatrope, and Saizen). In the Romer et al. study, the baseline-adjusted difference between Omnitrope and Genotropin for the change in HV was not statistically significant after nine months of treatment: –0.20 cm per year (95% confidence interval [CI], –1.34 to 0.94). Thus, the effect on HV of Genotropin and Omnitrope may be considered equivalent, given that the 95% CI did not exceed ± 2 cm per year. In addition, the Romer et al. study reported no statistically significant differences between Genotropin and Omnitrope for the outcomes of change in height and HtSDS over nine months: 0.23 cm (95% CI, –0.59 to 1.06) and 0.12 (95% CI, –0.06 to 0.30) respectively.

In the Shih et al. study, patients receiving Humatrope consistently underperformed those receiving Saizen or Genotropin in three linear growth measures (height, HtSDS, and HV). However, the study did not report the statistical significance of between-treatment differences and, given the small sample size, any such analyses are unlikely to provide meaningful results. Thus, the most credible results of comparative efficacy come from the Romer et al. study, which is restricted to the comparison of Genotropin and Omnitrope.

Additional limitations of the available data include the short duration of the trials and the uncertain relationship between short-term increases in growth and final adult height. In addition, the reviewed trials did not examine the impact of somatropin treatment on quality of life.

Harms

Harms appeared to be insufficiently reported in the Shih et al. trial. The assertion by Shih et al. that no adverse events were observed in the year-long trial appears to be suspect; it appears more likely that the incidence of adverse events was just not captured adequately. In the Romer et al. study, there were few notable differences in adverse events between Genotropin and Omnitrope except for hypothyroidism (none in the Genotropin group versus five in the Omnitrope group); however, the small sample size precludes definitive conclusions regarding the comparative safety. The increase in insulin-like growth factor-1 from baseline in the Genotropin group was slightly higher (between-group difference: 18.3 ng/mL versus Omnitrope) in the Romer et al. study; the observed between-treatment difference was not considered clinically meaningful.

Given the short duration and relatively small sample size, neither study provided meaningful data related to long-term harms, including mortality or malignancy outcomes. Observational data have suggested that persons treated with somatropin in childhood have a higher incidence of all-cause mortality compared with the general population; however, the role of somatropin in the higher incidence of mortality is unclear.

Other Considerations

A number of somatropin products available in Canada are indicated for the treatment of GHD in children, and they show similar pharmacokinetic/pharmacodynamic characteristics. The available products differ in terms of their dose formulation, injection devices, and cost. Choice of product is generally based upon patient and/or parent preference, in consultation with the clinician.

Pharmacoeconomic Summary

Somatropin (Genotropin) is available as an injection with multiple strengths (0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg syringes, and 5.3 mg and 12 mg pens). The manufacturer used a cost-minimization analysis to support its request for reimbursement of Genotropin for use in pediatric patients with GHD.[1] Similar clinical effectiveness for Genotropin and comparators was assumed based on the results of one trial comparing Genotropin to Omnitrope in children with GHD.[2] There were no published indirect comparisons of these agents. Based on Common Drug Review calculations using a confidential price of $[redacted] per milligram, the daily cost of the maximum dose of Genotropin ($[redacted]; 0.16 mg/kg to 0.24 mg/kg per week) is less than that of Humatrope ($77; 0.18 mg/kg to 0.30 mg/kg per week), Nutropin ($64; up to 0.3 mg/kg per week), Saizen ($59; 0.20 mg/kg to 0.24 mg/kg per week), and Omnitrope ($42; 0.025 mg/kg to 0.035 mg/kg per day).

Conclusions

The Common Drug Review identified two randomized controlled trials in children with GHD that compared Genotropin with other somatropin products available in Canada. The Shih et al. study was considered underpowered to provide meaningful results. Results of the Romer et al. study suggest Genotropin has similar effects on linear growth compared with Omnitrope over a period of nine months. There are insufficient data from the reviewed trials regarding the comparative efficacy and safety of Genotropin versus other somatropin products available in Canada, particularly in relation to final height, health-related quality of life, and infrequent or long-latency adverse events.

TABLE 1: SUMMARY OF RESULTS

Outcome	Romer et al.		Shih et al.		
	Genotropin N = 45	Omnitrope N = 44	Genotropin N = 5	Humatrope N = 5	Saizen N = 5
Height, cm					
Mean change from baseline	8.4	8.6	11.3	9.4	11.1
Difference in change between groups (95% CI)	0.23 (–0.59 to 1.06)		NR		
HV, cm per year					
Mean change from baseline	6.8	6.9	7.9	5.4	7.4
Difference in change between groups (95% CI)	–0.20 (–1.34 to 0.94)		NR		
HtSDS					
Mean change from baseline	0.67	0.73	1.33	0.66	1.06
Difference in change between groups (95% CI)	0.12 (–0.06 to 0.30)		NR		
HVSDS					
Mean change from baseline	7.28	8.14	NR		
Difference in change between groups (95% CI)	0.76 (–0.57 to 2.10)				
WDAEs, N (%)	0		0		
Subjects with SAEs, N (%)	NR		0		
IGF-1					
Mean change from baseline	172.6 ng/mL	154.3 ng/mL	0.74 U/mL	1.19 U/mL	1.47 U/mL
Difference in change between groups[a]	18.3		Genotropin: –0.45 versus Humatrope; –0.73 versus Saizen		

CI = confidence interval; HV = height velocity; HtSDS = height standard deviation score; HVSDS = height velocity standard deviation score; IGF-1 = insulin-like growth factor-1; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Calculated by the Common Drug Review (CDR).

1. INTRODUCTION

1.1 Disease Prevalence/Incidence

Growth hormone (GH) is produced by the pituitary gland and plays a role in achieving normal growth in children as well as in regulation of protein, lipid, and carbohydrate metabolism during both childhood and adult life.[3] Growth hormone deficiency (GHD) is the most common endocrine cause of short stature, although growth failure is associated with other causes as well, such as Turner syndrome, Prader-Willi syndrome, and chronic renal insufficiencies.[3] GHD may be isolated or may occur in association with deficiencies in other pituitary hormones.[3,4] The diagnosis of GHD is usually based on a combination of auxologic evaluation (persistently low growth rate when other identifiable causes, such as hypothyroidism, chronic illness, malnutrition, and genetic syndromes, have been ruled out), biochemical tests (GH stimulation tests) and neuroimaging of the hypothalamic-pituitary region.[5,6] The prevalence of GHD is estimated to be between 1 in 3,500 and 1 in 4,000 children in the United Kingdom.[3] According to a research paper published in 2012, approximately 20,000 children in the United States have been diagnosed with GHD.[7] There are no data on prevalence of GHD in Canada.

1.2 Standards of Therapy

Once the diagnosis of GHD is established in children, recombinant human growth hormone (also called somatropin) therapy is recommended as soon as possible in order to enhance growth velocity and normalize final adult height.[3,8] Previous observational studies indicated that somatropin is effective in children with GHD and, if started in early childhood, will normalize final height.[9,10] Somatropin products are considered safe for both short-term and long-term use,[5,11] and there are suggestions that the clinical effectiveness and safety profile of the various available somatropin products are similar.[7,12]

1.3 Drug

Genotropin's active ingredient is somatropin, which is produced through recombinant DNA technology. The amino acid sequence of Genotropin is identical to that of human growth hormone of pituitary origin, therefore stimulating linear growth in children; tissue growth (skeletal growth and cell growth); protein, carbohydrate, lipid, mineral and bone marker metabolism; and increasing serum insulin-like growth factor-1 (IGF-1).[13] Health Canada has approved Genotropin for the following indications:

- treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed
- the long-term treatment of children who have growth failure due to GHD
- replacement of endogenous growth hormone in adults with adult or childhood-onset GHD
- treatment of growth failure in short children born small for gestational age
- long-term treatment of idiopathic short stature.

This Common Drug Review (CDR) review report is specific to the manufacturer's submission for the indication of pediatric GHD.

The recommended dose of Genotropin for pediatric GHD is 0.16 mg/kg to 0.24 mg/kg body weight per week divided into six to seven doses and administered by subcutaneous injection. According to the product monograph, the dose of Genotropin should be adjusted based on the concentration of IGF-1 and adverse effects.[13] Genotropin is available in numerous dose formulations (0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg syringes, and 5.3 mg and 12 mg pens), intended for subcutaneous injection using one of the following devices: MiniQuick syringe or GoQuick pen.[13]

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The following somatropin products are approved by Health Canada: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, Norditropin, and Serostim. All (except Serostim, which is exclusively indicated for the treatment of HIV wasting associated with catabolism, weight loss, or cachexia) are indicated for the treatment of pediatric GHD. However, Norditropin does not appear to be marketed in Canada currently. A summary of all somatropin products approved by Health Canada, except Serostim, is provided in APPENDIX 4: CHARACTERISTICS OF SOMATROPIN PRODUCTS AVAILABLE IN CANADA.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of somatropin, specifically Genotropin, for the treatment of GHD in children.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Children with growth failure due to an inadequate secretion of endogenous growth hormone (GHD) Potential subgroups: isolated GHD versus multiple pituitary hormone deficiency
Intervention	Subcutaneous Genotropin 0.16 mg/kg to 0.24 mg/kg body weight per week (dosage is individualized based on patient's growth response)
Comparators	• Humatrope • Nutropin • Omnitrope • Saizen
Outcomes	**Efficacy outcomes** • Height (increase in height, final height) • HV • Quality of life by validated scales **Harms outcomes** Mortality, AEs, SAEs, WDAEs, harms of special interest (e.g., glucose intolerance, IGF-1 levels, malignancies)
Study Design	Published and unpublished RCTs with a study duration of at least six months

AE = adverse event; GHD = growth hormone deficiency; HV = height velocity; IGF-1 = insulin-like growth factor-1; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Genotropin and Growth Hormone Deficiency.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on July 19, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on November 20, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), including websites of regulatory agencies, health technology assessment agencies, and clinical guideline repositories. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See APPENDIX 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

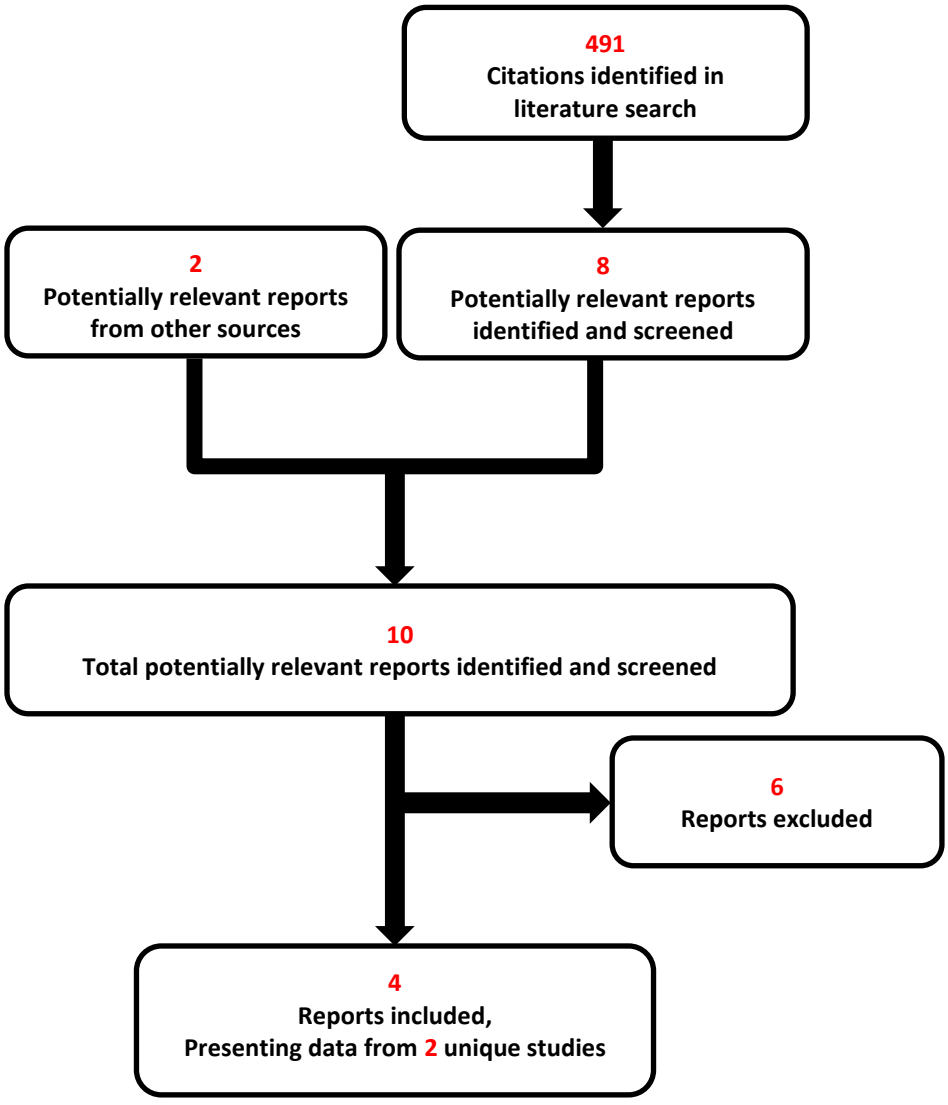
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 3: DETAILS OF INCLUDED STUDIES

		Romer et al.[14,15]	Shih et al.[16]
DESIGNS AND POPULATIONS	**Study design**	OL RCT	RCT (blinding not specified)
	Locations	Europe (Poland and Hungary)	Asia (Taiwan)
	No. of patients randomized (N)	89	15
	Inclusion criteria	2 to 14 years of age; prepubertal; idiopathic GHD; GH levels < 10 ng/mL in 2 provocation tests; treatment-naive; stipulated patient height of > 2 SDs below that of children of the same chronological age and sex; HV of < –1 SD over an interval of at least 6 months before enrolment; bone age retardation	Prepubertal; idiopathic GHD; GH levels < 10 ng/mL in provocation test; treatment-naive; patient height of > 2 SDs below that of children of the same chronological age; bone age retardation; adequate birth weight
	Exclusion criteria	Full-term birth weight < 2,500 g; chronic systemic disease; progression or recurrence of intracranial tumour in GHD secondary to intracranial lesion; idiopathic intracranial hypertension; chromosomal abnormalities; closed epiphyses; use of other growth-promoting medication	Systemic disease; malnutrition; dysmorphic syndrome; psychosocial disturbances
DRUGS	**Intervention**	Genotropin SC 0.03 mg/kg per day, doses were readjusted to each patient's body weight after 6 months	Genotropin SC 0.1 IU/kg per day (not clear whether the doses were adjusted)
	Comparator(s)	Omnitrope SC 0.03 mg/kg per day, doses were readjusted to each patient's body weight after 6 months	Humatrope SC 0.1 IU/kg per day (not clear whether the doses were adjusted) Saizen SC 0.2 IU/kg three times a week (not clear whether the doses were adjusted)
	Phase:		
	Active treatment	9 months	12 months
	Follow-up	All patients received Omnitrope after 9-month treatment	NR
OUTCOMES	**Primary end point**	Height, HtSDS, HV, and HVSDS at 9 months	Height, HV, and HtSDS at 12 months
	Other end points	Serum IGF-1 Safety	Somatomedin-C (also called IGF-1) Safety
NOTES	**Publications**[a]	Romer et al. 2007[14] Romer et al. 2009[15]	Shih et al. 1994[16]

GHD = growth hormone deficiency; HtSDS = height standard deviation score; HV = height velocity; HVSDS = height velocity standard deviation score; IGF-1 = insulin-like growth factor-1; NR = not reported; OL = open label; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation.

[a] One additional report (manufacturer's submission binder) was included.[2]

3.2 Included Studies

3.2.1 Description of Studies

Two head-to-head randomized controlled trials (RCTs) with parallel design that examined the efficacy and safety of Genotropin compared with other somatropin products were included in this review: one trial (Romer et al.[14,15]) comparing Genotropin with Omnitrope was conducted in Europe; another trial was carried out in Taiwan and compared Genotropin with both Humatrope and Saizen (Shih et al.[16]).

The Romer et al. study (N = 89) was an open-label, phase 3 RCT with an equivalence trial design, to evaluate the clinical efficacy and safety of Omnitrope versus Genotropin over nine months in children with GHD.[14,15] Thereafter, patients in the Genotropin group were switched to Omnitrope therapy. This CDR review reports results from the first nine months, during which Genotropin was compared with Omnitrope.

The Shih et al. study (N = 15) was a head-to-head RCT designed to assess the clinical efficacy and safety of a one-year treatment of Genotropin versus Humatrope or Saizen in children with GHD.[16] The study did not indicate whether patients or investigators were blind to treatment allocation.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The two studies had similar inclusion criteria: prepubertal children with idiopathic GHD (defined as GH levels < 10 ng/mL in provocation tests) who were treatment-naive were enrolled. Patients were excluded if their birth weight was less than 2,500 g or they had systemic disease. In the Romer et al. study, patients were also excluded if there was evidence of intracranial tumour growth or use of other growth-promoting medication. In the Shih et al. study, patients were ineligible if they experienced psychosocial disturbances.

b) Baseline Characteristics

In the Romer et al. study (Table 4), compared with Omnitrope-treated patients, those in the Genotropin group were slightly younger (mean age: 7.4 ± standard deviation [SD] 2.8 years versus 7.8 ± SD 2.6 years) and had a lower male-to-female ratio (21:24 versus 28:16). The Genotropin-treated patients were shorter than the Omnitrope-treated patients (mean height: 109.3 ± SD 15.7 cm versus 113.3 ± SD 13.3 cm). The differences in height may be related to the discrepancies in age and male-to-female ratio between the two treatment groups. However, both mean height SD scores (HtSDS) and height velocity SD scores (HVSDS) were balanced across the treatment groups.

In the Shih et al. study, patients in the Genotropin group were younger and shorter than in the groups receiving the other two somatropin products, Humatrope and Saizen. There were also between-group differences in HtSDS and height velocity (HV), which is not surprising given the small number of patients enrolled.

Patients in the Romer et al. study were two to three years younger than those in the Shih et al. study. The Romer et al. study enrolled Caucasians only, while the Shih et al. study enrolled Chinese children exclusively.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

	Romer et al. [14,15]		Shih et al. [16]		
	Genotropin N = 45	Omnitrope N = 44	Genotropin N = 5	Humatrope N = 5	Saizen N =5
Age, years (mean ± SD)	7.4 ± 2.8	7.8 ± 2.6	9.2 ± 2.3	10.3 ± 3.5	10.6 ± 1.7
Sex, males/females	21/24	28/16	2/3	4/1	3/2
Ethnic origin	All Caucasian		All Chinese		
Height, cm (mean ± SD)	109.3 ± 15.7	113.3 ± 13.3	106.2 ± 7.9	117.5 ± 12.6	117.0 ± 14.6
HtSDS (mean ± SD)	–3.10 ± 0.88	–2.95 ± 0.72	–4.03 ± 0.70	–2.88 ± 0.72	–4.16 ± 3.14
HV, cm per year (mean ± SD)	3.94 ± 0.82	3.83 ± 1.21	3.4 ± 0.7	4.0 ± 1.3	3.7 ± 1.2
HVSDS (mean ± SD)	–2.27 ± 0.93	–2.27 ± 1.23	NR		
Mean GH, ng/mL (mean ± SD)	3.82 ± 2.54	4.46 ± 2.72	NR		
IGF-1 (mean ± SD)	94.0 ± 64.2 ng/mL	95.5 ± 84.4 ng/mL	0.20 ± 0.16 U/mL	0.29 ± 0.13 U/mL	0.31 ± 0.33 U/mL

GH = growth hormone; HtSDS = height standard deviation score; HV = height velocity; HVSDS = height velocity standard deviation score; IGF-1 = insulin-like growth factor-1; SD = standard deviation.

3.2.3 Interventions

The Romer et al. study was an open-label study. Genotropin and Omnitrope were administered subcutaneously at a dose of 0.03 mg/kg per day for nine months, and the doses were adjusted to each patient's body weight. After nine months, all patients received Omnitrope, and treatment was continued until height was found to be satisfactory, epiphyseal fusion occurred, or the study was terminated (up to seven years of treatment).

In the Shih et al. study, patients were randomized to one of the three active treatment groups, Genotropin (0.1 IU/kg per day, equivalent to 0.03 mg/kg per day), Humatrope (0.1 IU/kg per day) or Saizen (0.2 IU/kg three times a week), for 12 months. The authors did not specify whether doses of somatropin were fixed or adjusted based on changes in weight.

The doses of somatropin products used in the two trials are consistent with Health Canada recommended doses for treatment of GHD in children.

3.2.4 Outcomes

a) Outcomes in the Romer et al. study:[14,15]

- Height was determined using a wall-mounted stadiometer (every three months). Standardization of height was based on national reference ranges of body height.
- HV was reported as centimeter per year based on a 12-month moving baseline of height values. Standardization of HV was based on means and SD of normally growing children taken from tables provided by Tanner et al.[17]

- HtSDS and HVSDS[14] were calculated using the formula SDS = (x1-x2) / SD, where x1 was the measured value, x2 was the mean value for the relevant chronological age and sex, and SD was for the relevant chronological age and sex.
- IGF-1 was measured by a central laboratory at baseline and at each scheduled visit.

b) Outcomes for the Shih study:[16]

- Outcomes were not explicitly defined.

3.2.5 Statistical Analysis

a) Efficacy Criteria

In the Romer et al. study, the objective of the nine-month comparative phase was to demonstrate that Omnitrope and Genotropin were similar in terms of efficacy and safety in children with growth failure secondary to GHD.[14] The primary outcomes were height, HtSDS, HV, and HVSDS. An equivalence margin was defined as ± 2.8 (corresponding to 1 SD of the HVSDS observed in a previous study with 12-month duration). This corresponds to an equivalence margin for HV of about 2 cm per year. A sample size of 40 patients per group was determined to be sufficient to detect a difference in HVSDS of 1 SD (2.8) between the treatment groups, with a power of 80% at the 5% level of significance. Analysis of covariance (ANCOVA) models was used to derive 95% confidence intervals (CIs) for the difference in mean height adjusted for baseline characteristics (although these baseline parameters were not specified), HSDS, HV, and HVSDS between Genotropin and Omnitrope. Analyses for efficacy parameters were performed on both intention-to-treat (ITT) and per-protocol (PP) populations, while only the ITT results were presented in the published article. However, ITT or PP was not defined in the article.

No sample size calculation was described in the Shih et al. study. It is unclear whether such calculation was performed before the study commenced. Paired t-tests were used in the statistical analysis.

b) Analysis Populations

ITT, PP and safety sets were not explicitly defined in either published study, and neither study described whether or how missing data were imputed. However, in the Romer et al. study, greater than 95% of patients in both treatment groups completed the nine-month treatment phase (see the following section).

3.3 Patient Disposition

In the Romer et al. study, 86 out of 89 patients completed the nine-month open-label treatment phase. The proportion of patients who withdrew from the study was 2.2% in the Genotropin group and 4.5% in the Omnitrope group. There were no withdrawals due to adverse events (AEs) reported during the treatment phase. The Shih et al. study did not report patient disposition data.

TABLE 5: PATIENT DISPOSITION

	Romer et al.[14,15]		Shih et al.[16]		
	Genotropin	Omnitrope	Genotropin	Humatrope	Saizen
Screened, N	NR		NR		
Randomized, N	45	44	5	5	5
Discontinued, N (%) **Protocol violations** **Noncompliance**	1 (2.2) 0 1	2 (4.5) 2 0	NR		
ITT, N (% of randomized)	45 (100)	44 (100)	NR		
PP, N (% of randomized)	NR	NR	NR		
Safety, N (% of randomized)	45 (100)	44 (100)	NR		

ITT = intention-to-treat; NR = not reported; PP = per-protocol.

3.4 Exposure to Study Treatments

In the Romer et al. study, treatment exposure was 34 patient-years for Genotropin and 32 patient-years for Omnitrope. No data were reported on exposure to study treatments in the Shih et al. study.

3.5 Critical Appraisal

3.5.1 Internal Validity

Strengths:

- In the Romer et al. study, allocation concealment was managed through central randomization.
- In the Romer et al. study, the frequency of study completion was high overall and was balanced between-treatment groups; greater than 95% of patients completed the nine-month trial in both Genotropin and Omnitrope treatment groups.
- In the Romer et al. study, the measurement of study outcomes was standardized through the use of a wall-mounted stadiometer for height measurements and the use of a central laboratory for determination of IGF-1 levels.

Limitations of the evidence:

- The methods of allocation concealment and randomization were not reported in the Shih et al. study; and it is unclear whether this was an open-label or blinded study.
- The Romer et al. study was an open-label study; however, given the objective nature of the study outcomes, this is unlikely to have resulted in bias.
- The equivalence margin in the Romer et al. study was defined based on the efficacy data from a single trial of Genotropin; however, the equivalence margin should be based on a range of values observed from existing studies in an appropriate patient population.
- No sample size calculation was reported for the Shih et al. study; however, given the small sample size, this study is expected to be underpowered to detect clinically meaningful differences. In addition, patient disposition was not reported, and there was no description of the method for handling missing data.
- The trials were of short duration, and thus would not be able to identify between-treatment differences in safety and efficacy that may manifest over the longer treatment durations used in clinical practice. In addition, the short duration and small sample sizes of the included trials do not allow for comparisons of final height, survival, or rare AEs. In both trials, no data were reported on quality of life, and limited data on safety.

- Both were manufacturer-sponsored studies. Generally speaking, studies sponsored by pharmaceutical companies are more likely to report outcomes favouring the sponsor than studies with other sponsors.

3.5.2 External Validity

According to the clinical expert consulted for this review, the results from the trials conducted in Europe and Asia may be generalized to the Canadian population. The selection criteria and patients' characteristics were reflective of a Canadian population. All participants were prepubertal children with mean age ranging from 7 to 11 years across the studies. The doses of Genotropin and the somatropin comparators used in the included trials were consistent with Health Canada–approved dosing. There were no results of subgroup analyses reported in either trial; however, given the small sample sizes in both trials, subgroup analyses are unlikely to be meaningful.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2).

3.6.1 Height

In the Romer et al. study, baseline height was similar in the Genotropin group and the Omnitrope groups (Table 6). Increases in height over nine months were 8.4 cm and 8.6 cm for the Genotropin and Omnitrope groups respectively. The baseline-adjusted difference (by ANCOVA model) in mean change in height between Genotropin and Omnitrope was statistically non-significant: 0.23 cm (95% CI, –0.59 to 1.06). HtSDS was another primary outcome in the Romer et al. study. Similar to height, the difference between Omnitrope and Genotropin in change in HtSDS from baseline to nine months was not statistically significant: 0.12 (95% CI, –0.06 to 0.30).

In the Shih et al. study, the mean changes in height from baseline to 12 months were 11.3 cm, 9.4 cm and 11.1 cm in Genotropin, Humatrope and Saizen-treated patients respectively. The statistical significance of these between-treatment differences was not reported.

3.6.2 Height Velocity (HV)

In the Romer et al. study, the baseline-adjusted difference between Omnitrope and Genotropin for the change in HV was not statistically significant after nine months of treatment: –0.20 cm per year (95% CI, –1.34 to 0.94). Thus, the effect on HV of Genotropin and Omnitrope may be considered equivalent, given that the 95% CI did not exceed ± 2 cm per year. Similar results were observed for HVSDS. The baseline-adjusted difference between Omnitrope and Genotropin for the change in HVSDS was not statistically significant after nine months of treatment: 0.76 (95% CI, –0.57 to 2.10).

In the Shih et al. study, HV at 12 months was statistically higher than before treatment ($P < 0.05$ for all three treatment groups). The changes in HV from baseline to study end (calculated by CDR) were 7.9 cm per year, 5.4 cm per year, and 7.4 cm per year for the Genotropin, Humatrope, and Saizen groups respectively. The statistical significance of between-treatment differences was not reported.

3.6.3 Health-Related Quality of Life

Health-related quality of life was not reported in either trial.

TABLE 6: KEY EFFICACY OUTCOMES

	Romer et al.[14,15]		Shih et al.[16]		
	Genotropin N = 45	Omnitrope N = 44	Genotropin N = 5	Humatrope N = 5	Saizen N = 5
HEIGHT, mean (SD), cm					
Baseline	109.3 (15.7)	113.3 (13.3)	106.2 (7.9)	117.5 (12.6)	117.0 (14.6)
Study end	117.7 (14.7)	121.9 (13.1)	117.5 (9.1)	126.9 (12.1)	128.1 (17.1)
Mean change from baseline[a]	8.4	8.6	11.3	9.4	11.1
Difference in change between groups (95% CI)	0.23 (–0.59 to 1.06) [b]		NR		
HV, mean (SD), cm per year					
Baseline	3.9 (0.8)	3.8 (1.2)	3.4 (0.7)	4.0 (1.3)	3.7 (1.2)
Study end	10.7 (2.9)	10.7 (2.6)	11.3 (2.0)	9.4 (1.9)	11.1 (3.3)
Mean change from baseline[a]	6.8	6.9	7.9	5.4	7.4
Difference in change between groups (95% CI)	–0.20 (–1.34 to 0.94) [b]		NR		
HTSDS, mean (SD)					
Baseline	–3.10 (0.88)	–2.95 (0.72)	–4.03 (0.70)	–2.88 (0.72)	–4.16 (3.14)
Study end	–2.43 (0.73)	–2.22 (0.68)	–2.70 (0.88)	–2.22 (0.99)	–3.10 (2.88)
Mean change from baseline[a]	0.67	0.73	1.33	0.66	1.06
Difference in change between groups (95% CI)	0.12 (–0.06 to 0.30) [b]		NR		
HVSDS, mean (SD)			NR		
Baseline	–2.27 (0.93)	–2.27 (1.23)			
Study end	5.01 (2.90)	5.87 (3.41)			
Mean change from baseline[a]	7.28	8.14			
Difference in change between groups (95% CI)	0.76 (–0.57 to 2.10) [b]				

CDR = Common Drug Review; CI = confidence interval; HV = height velocity; HtSDS = height standard deviation score; HVSDS = height velocity standard deviation score; NR = not reported; SD = standard deviation.

[a] Calculated by CDR.

[b] Baseline-adjusted difference in means between comparison groups by ANCOVA.

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2, Methods).

3.7.1 Adverse Events

In the Romer et al. study, the overall frequency of AEs (based on all enrolled patients) was not reported; however, the frequency of individual AEs (experienced by at least 5% of the enrolled population), including eosinophilia, elevated glycosylated hemoglobin, hematoma, and headache, was comparable between Genotropin and Omnitrope groups (Table 7). The majority of adverse reactions were reported to be mild in intensity.

No AEs were observed in the Shih et al. study.

3.7.2 Serious Adverse Events

There was one serious AE (SAE) reported in the Romer et al. study (worsening of existing scoliosis in a patient treated with Genotropin for nine months, and who received Omnitrope thereafter); however, it was unclear when this SAE occurred, during Genotropin therapy or Omnitrope therapy.

No SAEs were observed in the Shih et al. study.

3.7.3 Withdrawals due to Adverse Events

There were no withdrawals due to AEs in either study.

3.7.4 Mortality

Mortality was not reported in either trial.

3.7.5 Notable Harms

In the Romer et al. study, baseline serum IGF-1 levels were similar between the two treatment groups. The between-group difference in change from baseline in IGF-1 levels at study end was 18.3 ng/mL (calculated by CDR). IGF-1 levels were also increased after 12 months' somatropin therapy in all three treatment groups in the Shih et al. study.

Data related to other harms of interest, such as glucose intolerance or malignancies, were not available in the published articles.

TABLE 7: HARMS

	Romer et al.[14,15]		Shih et al.[16]		
	Genotropin N = 45	Omnitrope N = 44	Genotropin N = 5	Humatrope N = 5	Saizen N = 5
AEs					
Subjects with > 0 AEs	NR	NR	0	0	0
Most common AEs					
Hypothyroidism	NR	5 (11)	0		
Eosinophilia	3 (7)	5 (11)			
Increase in glycosylated hemoglobin	3 (7)	4 (9)			
Hematoma	4 (9)	3 (7)			
Headache	3 (7)	3 (7)			
Subjects with > 0 SAEs, N (%)	NR[a]		0	0	0
WDAEs, N (%)	0		0		
Deaths, N (%)	NR		NR		
Harms of interest					
IGF-1, mean (SD)					
Baseline	94.0 (64.2) ng/mL	95.5 (84.4) ng/mL	0.20 (0.16) U/mL	0.29 (0.13) U/mL	0.31 (0.33) U/mL
Study end	266.6 (192.0)	249.8 (184.0)	0.94 (0.72)	1.48 (0.73)	1.78 (1.50)
Mean change from baseline[b]	172.6	154.3	0.74	1.19	1.47
Difference in change between groups[b]	18.3		Genotropin: -0.45 versus Humatrope; -0.73 versus Saizen		

AE = adverse event; CI = confidence interval; IGF-1 = insulin-like growth factor-1; NR = not reported; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] 1 SAE (worsening of existing scoliosis) was reported in the Genotropin group in Romer et al. It is unclear whether this occurred during the Genotropin treatment phase or the Omnitrope therapy phase.

[b] Calculated by CDR.

4. DISCUSSION

4.1 Summary of Available Evidence

Two parallel, active-controlled RCTs were included in this review, one of which was designed as an equivalence trial. The other study did not specify whether it was a superiority, equivalence, or non-inferiority study. Both enrolled previously untreated pediatric patients with GHD (GH levels < 10 ng/mL in two provocation tests). Height-related outcomes were the primary outcomes in both studies. The Romer et al. study was conducted in Europe and compared Genotropin with Omnitrope during a nine-month treatment period. The Shih et al. study recruited Chinese patients exclusively, and compared Genotropin with Humatrope and Saizen at one year. Somatropin doses employed in the studies were consistent with Health Canada-recommended doses. The studies may be generalized to Canadian practice, according to the clinical expert consulted on this review.

Limitations of the included trials include the small number of patients enrolled and limited reported data related to AEs. These limitations were especially true of the Shih et al. study; thus, more weight should be put on the results of the Romer et al. study. In addition, the studies are limited by their short duration, which does not allow an assessment of the long-term benefits and harms of Genotropin, compared with other somatropin products. Finally, neither trial assessed the effect of somatropin treatment on health-related quality of life.

4.2 Interpretation of Results

4.2.1 Efficacy

In the two included trials, the mean increase in height from baseline to the study end (ninth or twelfth month) in children with GHD ranged from 8 cm to 11 cm across the somatropin products (Genotropin, Omnitrope, Humatrope, and Saizen). In the Romer et al. study, the change in height and HtSDS from baseline did not differ statistically between Genotropin and Omnitrope, and both products were considered equivalent based on HV.

In the Shih et al. study, Humatrope-treated patients consistently underperformed those treated with Saizen and Genotropin in three linear growth measures (height, HtSDS, and HV). However the study did not report the statistical significance of between-treatment differences and, given the small sample size, any such analyses are unlikely to provide meaningful results. Thus, the most credible results of comparative efficacy come from the Romer et al. study, which is restricted to the comparison of Genotropin and Omnitrope.

In the Romer et al. study, the low withdrawal rate and objective nature of the outcome measures provide some confidence in the internal validity of study findings despite the open-label design. However, a number of limitations should be noted. The comparison between Genotropin and Omnitrope was limited to nine months, which may not be sufficient for clinically important differences between study drugs to manifest. Further, the relationship between short-term increases in growth and final adult height, which is an important clinical outcome, is unclear, and the trial did not study the impact of treatment on quality of life.

While the Romer et al. trial suggests that Genotropin has similar efficacy to that of Omnitrope, the trial does not provide evidence of the benefit of treatment versus no treatment in children with GHD. In a recent health technology assessment,[18] Takeda et al. assessed the clinical effectiveness and cost-effectiveness of somatropin compared with treatment strategies without somatropin for GHD and other conditions related to growth disorders in children. One RCT was included in this health technology assessment for pediatric GHD, and the findings showed that the children in the somatropin group grew 2.7 cm faster per year than those in the untreated group; the difference was statistically significant. Details are provided in APPENDIX 5: FINDINGS FROM SYSTEMATIC REVIEWS OF SOMATROPIN IN THE TREATMENT OF GHD IN CHILDREN.

In addition, data from a retrospective review of children treated with somatropin (Humatrope, Nutropin, and Saizen) for idiopathic GHD indicated that final adult heights within 2 standard deviation score (SDS) of the population range were achieved in 84% of the patients, and the average final adult height was 0.5 SDS below midparental height targets. All patients in this study received somatropin; thus, there were no data on non-treated children.[9] Other studies presented similar findings for final height associated with somatropin therapy.[10,19]

4.2.2 Harms

Harms appeared to be insufficiently reported in the Shih et al. trial. The assertion by Shih et al. that no AEs were observed in the year-long trial appears to be suspect; it appears more likely that the incidence of AEs was not captured adequately. In the Romer et al. study, there were few notable differences in AEs between Genotropin and Omnitrope except for hypothyroidism (none in the Genotropin group versus five in the Omnitrope group); however, the relatively small sample size precludes definitive conclusions regarding the comparative safety.

IGF-1 is a mitogen and may be associated with increasing risk of certain types of cancer.[5,20] On the other hand, baseline IGF-1 and change in IGF-1 during treatment with somatropin are correlated with the growth response. Therefore, IGF-1 concentrations should be monitored regularly during the treatment, and the dose of somatropin should be titrated according to the levels of IGF-1, which should not exceed the upper limit of normal IGF-1 levels matched to age and sex.[5,13] In the Romer et al. study, the increase in IGF-1 from baseline in the Genotropin group was slightly higher (between-group difference: 18.3 ng/mL versus Omnitrope) in the Romer et al. study, but lower (between-group differences: –0.45 U/mL versus Humatrope, –0.73 U/mL versus Saizen) in the Shih et al. study. According to the clinical expert consulted for this review, these differences were not considered clinically meaningful.

Given the short duration and relatively small sample size, neither study could be expected to provide meaningful data related to mortality or malignancy outcomes. Non-randomized trials have provided some evidence on these outcomes. A population-based cohort study conducted in France compared the incidence of mortality in patients treated with somatropin in childhood for idiopathic isolated GHD (75% of the study population), neurosecretory dysfunction, idiopathic short stature, or born short for gestational age, with the general French population. Within-cohort comparisons were performed as well, such as all-cause mortality in somatropin doses > 50 mcg/kg per day versus the lowest dose category.[21] The mean treatment duration was 3.9 ± 2.6 years, and the mean follow-up was 7.8 ± 5.2 years. All-cause mortality was statistically greater in somatropin-treated patients (standardized mortality ratio [SMR] 1.33, 95% CI, 1.08 to 1.64) compared with the general population; however, the role of somatropin in the higher incidence of mortality is unclear. However, high-dose somatropin (> 50 mcg/kg per day) was associated with higher mortality rates (SMR 2.94, 95% CI, 1.22 to 7.07) than low-dose somatropin (≤ 20 mcg/kg per day). Compared with the general population, all-type cancer-

related mortality was not increased; however, bone tumour–related mortality was increased (SMR 5.00, 95% CI, 1.01 to 14.63), as well as death related to cerebral hemorrhage (SMR 6.66, 95% CI, 1.79 to 17.05). Another observational study reported the incidence of cancer in patients treated with Genotropin specifically.[20] The mean treatment duration of Genotropin therapy before the diagnosis of cancer was 3.6 years; the standardized incidence ratio of new malignant neoplasm was 1.26 (95% CI, 0.86 to 1.78), compared with the general population.

4.3 Other Considerations

A number of somatropin products available in Canada are indicated for the treatment of GHD in children. The available products show similar pharmacokinetic/pharmacodynamic characteristics (APPENDIX 4: CHARACTERISTICS OF SOMATROPIN PRODUCTS AVAILABLE IN CANADA), which are supportive of the conclusion of similar efficacy, as reported in the Romer et al. study. However, the available somatropin products differ in terms of their formulation (stabilized solution or powder for reconstitution), injection devices (syringes versus pens), and cost. The clinical expert consulted for this review indicated that clinicians consider the various somatropin products to be equally efficacious and safe, that the choice of product is generally based upon patient and/or parent preference in consultation with the clinician, and that switching between products is uncommon. However, because of the difference in the recommended dose between Genotropin and other somatropin products indicated for GHD in children, there is the potential for dosing errors when switching between products.

5. CONCLUSIONS

The CDR identified two RCTs in children with GHD that compared Genotropin with other somatropin products available in Canada. The Shih et al. study was considered underpowered to provide meaningful results. Results of the Romer et al. study suggest Genotropin has similar effects on linear growth compared with Omnitrope over a period of nine months. There are insufficient data from the reviewed trials to compare efficacy and safety of Genotropin with other somatropin products available in Canada, particularly related to final height, health-related quality of life, and infrequent or long-latency AEs.

APPENDIX 1: PATIENT INPUT SUMMARY

No patient input was received regarding the use of Genotropin (somatropin) for pediatric growth hormone deficiency.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2013 July 19 Ovid MEDLINE In-Process & Other Non-Indexed Citations Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 19, 2013
Alerts:	Weekly search updates began July 19, 2013 and ran until November 20, 2013.
Study Types:	No filters used.
Limits:	No date or language limits used. Conference abstracts excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	Subject headings
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.af	All fields
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
.tn	Drug trade name
.mf	Drug manufacturer

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	(CB-311 or LY-137998 or SJ-0011 or SR-29001 or CB311 or LY137998 or SJ0011 or SR29001).ti,ot,ab,sh,rn,hw,nm.
2	(genotropin* or genotonorm*).ti,ab,ot,sh,rn,hw,nm,tn.
3	1 or 2
4	3 use pmez
5	(CB-311 or LY-137998 or SJ-0011 or SR-29001 or CB311 or LY137998 or SJ0011 or SR29001).ti,ab.
6	(genotropin* or genotonorm*).ti,ab.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	exp *human growth hormone/ or exp *growth hormone derivative/ or exp *recombinant growth hormone/
11	(human growth hormone* or hgh or r-hgh or rhgh).ti,ab.
12	somatrop*.ti,ab.
13	exp *somatropin/
14	10 or 11 or 12 or 13
15	(pfizer or upjohn or pharmacia).ti,ab,ot,hw,rn,nm,tn.
16	14 and 15
17	9 or 16
18	*growth hormone deficiency/
19	(growth adj3 hormone* adj7 (deficien* or failure* or therap* or replacem* or insufficien* or treatment* or disturbance* or disorder*)).ti,ab,hw.
20	(hyposomatotropinism or somatotropin deficiency or somatotropin insufficiency).ti,ab.
21	*pituitary dwarfism/
22	((hypophys* or pituitary or hypopituitary or hyposomatotropic) adj5 (dwarf* or infantilism or nanism or short stature)).ti,ab.
23	(growth adj2 failure).ti,ab.
24	((gh or rhgh or hgh) adj2 (deficien* or failure* or therap* or replacem* or insufficien* or treatment* or disturbance* or disorder*)).ti,ab.
25	18 or 19 or 20 or 21 or 22 or 23 or 24
26	17 and 25
27	26 not conference abstract.pt.
28	exp animals/
29	exp animal experimentation/ or exp animal experiment/
30	exp models animal/
31	nonhuman/
32	exp vertebrate/ or exp vertebrates/
33	animal.po.
34	or/28-33

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
35	exp humans/
36	exp human experimentation/ or exp human experiment/
37	human.po.
38	or/35-37
39	34 not 38
40	27 not 39
41	remove duplicates from 40

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and other)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 2013
Keywords:	Included terms for Genotropin and Growth Hormone Deficiency
Limits:	No date or language limits used.

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Inappropriate Comparator

1. Coelho R, et al. Horm Res. 2008;70(2):85-8.
2. Drake WM, et al. J Clin Endocrinol Metab [Internet]. 2003 Apr [cited 2013 Aug 9];88(4):1658-63. Available from: http://jcem.endojournals.org/cgi/reprint/88/4/1658
3. Mauras N, et al. J Clin Endocrinol Metab [Internet]. 2005 Jul [cited 2013 Aug 9];90(7):3946-55. Available from: http://jcem.endojournals.org/cgi/reprint/90/7/3946

Not English

1. Dorantes-Alvarez LM. Bol Med Hosp Infant Mex. 1990 Jun;47(6):369-71. In Spanish.

Study Design (Not Randomized Controlled Trial)

1. Wilton P, et al. J Pediatr. 2010 Aug;157(2):265-70.
2. Wu KH, et al. Ann Hematol. 2003 Oct;82(10):637-40.

APPENDIX 4: CHARACTERISTICS OF SOMATROPIN PRODUCTS AVAILABLE IN CANADA

Aim

To summarize the similarities and differences among the somatropin products available in Canada.

Findings

The following somatropin products are presented in this section: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin. Serostim, another somatropin product available in Canada, has been omitted from this comparison because it is exclusively indicated for the treatment of HIV wasting associated with catabolism, weight loss, or cachexia. The information presented in the following tables was obtained from the current Canadian product monographs.[13,22-28] It is important to note that the respective monographs have slight differences in the content, layout, and types of information. This is likely due to differences in product monograph requirements at the time of approval.

Manufacturing Information, Formulations, Indications, and Dosing

As illustrated in Table 8, all products use recombinant DNA technology in *Escherichia coli* host cells except Saizen, which is produced in mammalian source host cells. Biological activity was not reported for all products, but, when reported, it is 3 IU = 1 mg. Although not always reported, it is likely that all products contain some host cell impurities in the final formulation. The excipients used as preservatives or stabilizers vary greatly between formulations (lyophilized powder and solution) as well as among products. Some of the products contain benzyl alcohol, which is contraindicated in newborns. While all products except Norditropin are indicated for the treatment of growth hormone deficiency in both children and adults, several of the products have additional indications for the treatment of Turner syndrome, idiopathic short stature, children born small for gestational age, chronic renal insufficiency or failure, and short stature homeobox-containing gene deficiency.

All products, except Omnitrope and Norditropin, offer a lyophilized powder formulation that requires reconstitution before administration (see Table 9). In addition, several products offer a stabilized solution either in a vial or in a pen with a cartridge ready for injection. All products are recommended for subcutaneous injection, and Nutropin, Humatrope, and Saizen can also be administered by intramuscular injection. The proprietary products are variable in their concentrations and administration formats. This is consistent with the variability in the recommended dosing for the different products, although the dosing recommendations for pediatric GHD and Turner syndrome appear to be more consistent among products than those for adult GHD. The inconsistency in formulations and in dosing recommendations adds to the complexity when a patient is switched from one product to another and could increase the potential for dosing errors.

TABLE 8: DESCRIPTION OF SOMATROPIN PRODUCTS

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Genotropin	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human growth hormone gene	Not mentioned	Preparations of Genotropin contain a very small amount of periplasmic *E. coli* peptides (PECP).	5.8 mg, 5.3 mg, and 12 mg per pen cartridge: glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, metacresol and water for injection	Pediatric GHD, SGA, TS, ISS, and adult GHD
				0.2 mg to 2.0 mg per syringe: glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, and water for injection	
Omnitrope	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human growth hormone gene	3.0 IU/1 mg	Contains small amount of host cell *E. coli* peptide (HCP)	5.8 mg per vial: glycine, disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dehydrate, and diluent supplied bacteriostatic water containing 1.5% benzyl alcohol	Pediatric and adult GHD
				5 mg per 1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, mannitol, benzyl alcohol, and water for injection	
				10 mg per 1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, phenol, glycine, and water for injection	

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Humatrope	Recombinant DNA technology Use *E. coli,* which is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	5.0 mg per vial: mannitol, glycine, dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide may have been used for pH adjustment, water for injection with glycerin and metacresol	Pediatric GHD, SHOX deficiency, TS, ISS, SGA and adult GHD
				6 mg, 12 mg, and 24 mg cartridges: mannitol, glycine, dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide may have been added to adjust the pH, water for injection, metacresol and glycerin	
Nutropin	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	10.0 mg per vial: glycine, mannitol, sodium phosphate dibasic, sodium phosphate monobasic, and benzyl alcohol	Pediatric GHD, growth failure due to renal insufficiency, TS, and adult GHD
				10 mg per 2 mL vial: phenol, polysorbate 20, sodium chloride, sodium citrate	
				10 mg per 2 mL pen cartridge: phenol, polysorbate 20, sodium chloride, sodium citrate	
				5 mg per 2 mL, 10 mg per 2 mL and 20 mg per 2 mL NuSpin cartridge: phenol, polysorbate 20, sodium chloride, sodium citrate	

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Saizen	Recombinant DNA technology Use mammalian cell expression system (C127 mouse cells)	3.0 IU/1 mg	Not mentioned	3.3 mg per vial: mannitol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate	Pediatric GHD, SGA, TS, chronic renal failure, and adult GHD
				5mg per vial: phosphoric acid, sodium hydroxide, sucrose	
				8.8 mg (5.83 mg/mL) click.easy: phosphoric acid, sodium hydroxide, sucrose, and cartridge of bacteriostatic solvent	
				6 mg (5.83 mg/mL), 12 mg (8 mg/mL), and 20 mg (8 mg/mL) cartridges: citric acid, phenol, poloxamer 188, and sucrose	
Norditropin	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	5 mg per 1.5 mL, 10 mg per 1.5 mL, and 15 mg per 1.5 mL cartridges or pens: histidine, poloxamer 188, phenol, mannitol, HCl/NaOH, and water for injection	Pediatric GHD and SGA

E-Coli = *Escherichia coli*; GHD = growth hormone deficiency; HCl = hydrogen chloride; HCP = host cell proteins; ISS = idiopathic short stature; NaOH = sodium hydroxide; PECP = periplasmic *E. coli* peptides; SGA = small for gestational age; SHOX = short-stature homeobox-containing gene; TS = Turner syndrome.

TABLE 9: PHYSICAL DESCRIPTION AND DOSING OF SOMATROPIN PRODUCTS

Drug	Formulation	Strength	Administration	Dosing		
				Pediatric GHD	Adult GHD	Turner Syndrome
Genotropin	Lyo powder in a 2-chamber pen cartridge	5 mg, 5.3 mg, and 12 mg per pen	Reconstitution and then SC injection	0.16 mg/kg to 0.24mg/kg per week divided into 6 to 7 SC injections per week	0.15 mg to 0.3 mg per day to a maximum of 1.33 mg per day	0.33 mg/kg per week divided into 6 to 7 SC injections
	Lyo powder in a 2-chamber glass cartridge	0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg and 2.0 mg per syringe				
Omnitrope	Lyo powder[a]	5.8 mg per vial	Reconstitution and then SC injection	0.025 mg/kg to 0.035 mg/kg per day	0.15 mg to 0.3 mg per day to a maximum of 1.33 mg per day	No indication
	Solution in pen cartridges	5mg per 1.5 mL, 10 mg per 1.5mL	SC injection			
Humatrope	Lyo powder	5.0 mg per vial	Reconstitution and then SC or IM injection	0.18 mg/kg per week given on 3 alternate days or 6 to 7 injections per week to a maximum of 0.3 mg/kg week	Start dose of 0.006 mg/kg per day Maximum dose 0.0125 mg/kg per day	0.375 mg/kg per week given on 3 alternate days or daily
	Lyo powder cartridge and diluent syringe	6 mg, 12 mg and 24 mg per cartridge				
Nutropin	Lyo powder	10 mg per vial	Reconstitution and then IM or SC injection	Up to 0.3 mg/kg per week divided into 7 injections per week	Start dose of 0.042 mg/kg per week Maximum dose 0.175 mg/kg per week in patients under 35 and maximum dose 0.0875 mg/kg per week in patients over 35 divided into 7 injections per week	Up to 0.375mg/kg week divided into equal doses 3 to 7 injections per week by subcutaneous injection
	Solution	10 mg per 2mL vial	IM or SC injection			
	Solution in pen cartridge	10 mg per 2mL pen cartridge	SC injection			
	Solution in NuSpin injection device	5 mg per 2 mL, 10 mg per 2 mL, or 20 mg per 2 mL cartridges	SC injection			

Drug	Formulation	Strength	Administration	Dosing		
				Pediatric GHD	Adult GHD	Turner Syndrome
Saizen	Lyo powder	3.33 mg per vial and 5 mg per vial	Reconstitution and then IM or SC injection	0.2 mg/kg to 0.27 mg/kg per week	Start dose of 0.005 mg/kg per day Dose may be increased to 0.01 mg/kg per day after 4 weeks	0.375 mg/kg per week
	Lyo powder in a click.easy	8.8 mg (5.83 mg/mL) per click.easy	Reconstitution and then SC injection			
	Solution for injection in a cartridge	6 mg (5.83 mg/mL), 12 mg (8 mg/mL), 20 mg (8 mg/mL) per cartridge	SC injection			
Norditropin	Solution for injection in a cartridge	5 mg per 1.5 mL, 10 mg per 1.5 mL and 15 mg per 1.5 mL per cartridge	SC injection	Daily up to 0.043 mg/kg per day		
	Solution for injection in pen	5 mg per 1.5 mL, 10 mg per 1.5 mL and 15 mg per 1.5 mL per pen	SC injection			

GHD = growth hormone deficiency; IM = intramuscular; lyo = lyophilized; SC = subcutaneous.
[a] Lyophilized powder not marketed in Canada.

Pharmacokinetics/Pharmacodynamics

Although there are slight differences in the pharmacokinetic profiles of the different somatropin products based on the available information (Table 10), these differences do not appear to be significant and are not expected to result in important clinical consequences. There is limited information on the pharmacodynamic properties of the other somatropin products in Canada. Omnitrope appears to have very similar pharmacodynamic properties to Genotropin (Table 11).

TABLE 10: PHARMACOKINETIC PROFILE OF SOMATROPIN PRODUCTS

Pharmacokinetics	AUC (h-mcg/L ± SD)	C_{max} (mcg/L ± SD)	T_{max} (h)	$T_{1/2}$ (h ± SD)	Bioavailability (%)	Clearance (L per hour per kg)	Metabolism
Genotropin 5 mg of 5.8 mg per vial Lyo powder	592 ± 131[a]	78 ± 27[a]	4 (95% CI, 2.0 to 8.0)[a]	2.6 ± 0.7[a]	Approx. 80%	NR	Liver and kidneys
Omnitrope[a] 5 mg of 5.8 mg per vial Lyo powder	566 ± 147	71 ± 24	4.0 (95% CI, 2.0 to 6.0)	3.2 ± 0.7	Approx. 80%	0.14 (± 0.04)	Liver and kidneys
5 mg of 5 mg per 1.5 mL solution	546 ± 140	72 ± 28	4.0 (95% CI, 2.0 to 8.0)	2.8 ± 0.7			
Humatrope	NR	NR	NR	3.8 for SC and 4.9 for IM	Approx. 75% after SC and 63% after IM	0.14	Liver and kidneys
Nutropin 0.1 mg of Lyo powder	626	56.1	7.5	7.5	NR	0.116 to 0.174	Liver and kidneys
0.1 mg of solution	673	71.1	3.9	2.3		0.116 to 0.174	
0.05 mg of solution	486	72.5	4.2	2.22		0.106	
Saizen Lyo powder 8.8 mg	320 (95% CI, 205 to 495)	45.1 (95% CI, 21.5 to 69.2)	4 (95% CI, 2.0 to 7.0)	2.7 (95% CI, 1.2 to 5.8)	70% to 90%	15 L per hour	NR
Norditropin 2.5 mg/m^2 (0.085 mg/kg)	397 to 408	42 to 46	4	2.6	NR	0.072 to 0.234	Liver and kidneys
5 mg (0.054 to 0.082 mg/kg)	396 to 433	39 to 43	4 to 4.5	3			

AUC = area under the concentration curve; C_{max} = maximum plasma concentration of drug; CI = confidence interval; IM = intramuscular; lyo = lyophilized; NR = not reported; SC = subcutaneous; T_{max} = time to reach maximum concentration of the drug; $T_{1/2}$ = drug half-life.

[a] Data from comparative pharmacokinetic/pharmacodynamic trial of Omnitrope versus Genotropin (EP00-104).

TABLE 11: PHARMACODYNAMIC PROFILE OF RECOMBINANT HUMAN GROWTH HORMONE PRODUCTS

Pharmacodynamics IGF-1	AUEC (h-mcg/L ± SD)	E_{max} (mcg/L)	T_{maxE} (h)
Genotropin[a] 5 mg of 5.8 mg per vial Lyo powder	15,960 ± 3,557	209 ± 49	24 (95% CI, 12 to 48)
Omnitrope[a] 5 mg of 5.8 mg per vial Lyo powder	16,712 ± 3,847	218 ± 56	24 (95% CI, 12 to 48)
5 mg of 5 mg per 1.5 mL solution	16,295 ± 3,664	213 ± 49	24 (95% CI, 12 to 48)
Humatrope	NR	NR	NR
Nutropin	NR	NR	NR
Saizen	NR	NR	NR
Norditropin 0.0009 mg/kg to 0.009 mg/kg	NR	241	NR

AUEC = area under the effective concentration curve; CI = confidence interval; E_{max} = maximum effect of drug; IGF-1 = insulin-like growth factor-1; lyo = lyophilized; NR = not reported; T_{maxE} = time to reach maximum effect of the drug.
[a] Data from comparative pharmacokinetic/pharmacodynamic trial of Omnitrope versus Genotropin (EP00-104).

Conclusion

The somatropin products indicated for the treatment of GHD have some differences in dosage forms and recommended dose, but have similar pharmacokinetic and pharmacodynamic profiles.

APPENDIX 5: FINDINGS FROM SYSTEMATIC REVIEWS OF SOMATROPIN IN THE TREATMENT OF GHD IN CHILDREN

Aim

To summarize the findings from systematic reviews of the efficacy and safety of somatropin in children with GHD.

Findings

A health technology assessment by Takeda et al. (Table 12) assessed the clinical effectiveness and cost-effectiveness of somatropin compared with treatment strategies without somatropin for children with GHD, Turner syndrome, and other conditions resulting in growth failure.[18] One unblinded randomized controlled trial (RCT) was identified for the treatment of pediatric GHD. It was not specified which somatropin product was used in this trial. The study reported significantly increased growth velocity and higher serum insulin-like growth factor-1 levels in somatropin-treated patients compared with no somatropin therapy. This report was not industry sponsored.

One systematic review conducted by Loftus et al. evaluated the clinical efficacy and effectiveness of Genotropin in children with short stature, including those with GHD (Table 12).[29] Three RCTs in children with GHD were included in this review. One of them (Romer et al. 2007[14,15]) was included in the current CDR review. The other two RCTs compared different doses of Genotropin, or different Genotropin devices. The Loftus review was sponsored by Pfizer Ltd., the manufacturer of Genotropin.

TABLE 12: EVIDENCE FROM SYSTEMATIC REVIEWS ON LONG-TERM EFFICACY AND SAFETY OF SOMATROPIN THERAPY FOR CHILDREN WITH GHD

Study	Search Dates, Selection Criteria	No. of Included Studies	Main Findings	Authors' Conclusion
Takeda et al. 2010[18]	Multiple databases were searched until June 2009. RCTs and systematic reviews of RCTs of any duration; patients < 16 years, with growth failure due to GHD or other conditions, and treated with somatropin; English studies only	28 RCTs (1 unblinded RCT on pediatric GHD) and systematic reviews of RCTs	The only RCT compared different doses of somatropin or placebo for 1 year. <u>Growth velocity:</u> somatropin group grew 2.7 cm per year faster than those in the untreated group, $P < 0.05$ <u>IGF-1 (± SD):</u> 91.2 ± 30.4 ng/mL in somatropin group versus 49.4 ± 19 ng/mL in the untreated group, $P < 0.05$ No data on final height, QoL or safety	Statistically significant improvement in height outcomes were observed in somatropin-treated patients.

Study	Search Dates, Selection Criteria	No. of Included Studies	Main Findings	Authors' Conclusion
Loftus et al. 2010[29]	Multiple databases were searched until January 2009. RCTs and observational studies, systematic reviews of any duration; patients < 16 years and treated with Genotropin; English studies only	30 RCTs (3 were for pediatric GHD) and 37 observational studies	See the findings of efficacy and safety from the Romer et al. study in the main report, when Genotropin was compared with Omnitrope in 9 months' therapy (Tables 7 and 8 in the main report).	A lack of long-term RCTs reporting final height data and other important health outcomes, i.e., QoL

GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation.

Conclusion

Systematic reviews of clinical effectiveness and safety of somatropin therapy in children with GHD reported favourable results for somatropin, when compared with no treatment, or equivalent efficacy and safety between Genotropin and another somatropin – Omnitrope. However, long-term data are lacking, particular for clinically meaningful outcomes such as final height and health-related quality of life.

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