Common Drug Review
Clinical Review Report

January 2014

Drug	somatropin (Genotropin) (0.15 mg/day to 0.3 mg/day)
Indication	Replacement of endogenous growth hormone in adults with growth hormone deficiency
Listing request	List in the same manner as other currently listed somatropin products
Manufacturer	Pfizer Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

BMD	bone mineral density
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CI	confidence interval
GH	growth hormone
GHD	growth hormone deficiency
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HDL	high-density lipoprotein
HRQoL	health-related quality of life
IGF-1	insulin-like growth factor-1
LDL	low-density lipoprotein
MCID	minimal clinically important difference
NHP	Nottingham Health Profile
PGWBI	Psychological General Well-Being Index
QoL–AGHDA	Quality of Life–Assessment of Growth Hormone Deficiency in Adults
RCT	randomized controlled trial
RR	relative risk
TC	total cholesterol
WMD	weighted mean difference

EXECUTIVE SUMMARY

Introduction

Growth hormone (GH) plays a role in the regulation of protein, lipid, and carbohydrate metabolism during adult life. About three-quarters of adult growth hormone deficiency (GHD) cases are associated with pituitary tumours and subsequent surgery and radiotherapy. Clinical manifestations of GHD in adults include decreased lean body and muscle mass, increased fat mass, reduced bone mineral density, lipid profile changes, and psychiatric symptoms. Diagnosis of adult GHD is usually based on a medical history (childhood-onset GHD, hypothalamic–pituitary disease or surgery, cranial irradiation or traumatic brain injury) and biochemical tests (GH stimulation tests). In a European study, the prevalence of hypopituitarism was estimated to be 29 to 45 per 100,000, and the incidence 4.2 cases per 100,000. There are no data on prevalence or incidence of GHD in Canada.

Once diagnosed, patients with GHD may receive replacement therapy with somatropin, which is identical in amino acid sequence to endogenous GH and synthesized through recombinant DNA technology. The goals of replacement therapy are to correct the metabolic, functional, and psychological abnormalities associated with adult GHD. A number of somatropin products are available in Canada for replacement of endogenous growth hormone in adults with GHD, including Genotropin. The approved dose of Genotropin in this population is 0.15 mg to 0.3 mg per day, administered subcutaneously.

Results and Interpretation

No randomized controlled trials (RCTs) comparing Genotropin with other somatropin drugs available in Canada in adults with GHD were identified. Common Drug Review (CDR), in consultation with the clinical expert contracted for the review, identified three key clinical issues of relevance to consideration of Genotropin treatment in adults with GHD: a summary of systematic reviews of somatropin in adult GHD; comparison of the pharmaceutical, pharmacokinetic, and pharmacodynamic characteristics of somatropin products available in Canada; and a summary of manufacturer-submitted placebo-controlled RCTs of Genotropin.

Summary of Systematic Reviews of Somatropin

Eight systematic reviews comparing somatropin with placebo or no treatment were included, and data on key efficacy and safety parameters (as identified a priori in the protocol for the CDR review) were summarized. The number of included individual studies ranged from 8 to 54. The included studies in these reviews varied with respect to study design (RCT, non-randomized comparative studies, and observational studies, etc.), quality of evidence, patient characteristics, and outcome measures of interest. Meta-analysis was performed in six reviews. Data on survival were assessed in only one systematic review; however, no data on cardiovascular morbidity were reported. Most of the reviews did not differentiate between various somatropin products. In one systematic review that specifically indicated that Genotropin was one of the study drugs, the dose used in the included studies (ranging from 0.4 mg to 1.8 mg per day) was generally higher than the dose approved in Canada.

Efficacy

Two systematic reviews of RCTs and non-RCTs reported findings on health-related quality of life (HRQoL) in adults with GHD. Inconsistent results were presented. Some studies indicated that long-term or short-term somatropin therapy was associated with improvement in HRQoL, mainly energy levels, while other studies reported no difference between somatropin and placebo. Numerical results were not provided

in these two reviews, and minimal clinically important differences are not available; hence, the clinical significance of the observed differences (where they existed) could not be determined.

Two meta-analyses of RCTs reported findings on exercise capacity. Both suggested statistically significant improvements for patients who received 3 to 18 months of somatropin therapy, compared with placebo. The expert consulted by CDR considered the improvements in exercise capacity to be of moderate clinical significance.

Pooled data in two meta-analyses of RCTs showed no significant difference in muscle strength between 3 to 12 months of somatropin and placebo; in addition, long-term (5 to 10 years) results from non-RCTs and observational studies suggested that somatropin improved muscle strength during the first five years of treatment, but the effect was not sustained after five years.

Three reviews reporting lipid profiles from RCTs and non-RCTs indicated that, in some of the included trials, somatropin therapy was associated with lower levels of total cholesterol and low-density lipoprotein compared with no treatment or placebo, while other trials did not detect a significant between-group difference in these parameters.

A positive impact of somatropin therapy on bone mineral density in different sites was demonstrated in one meta-analysis of RCTs and non-RCTs; however, its long-term (ranging from 5 to 15 years) effect on bone mineral density varied from trial to trial in another systematic review. Fractures were infrequently reported, and the clinical significance of the observed bone mineral density improvements is uncertain.

Statistically significantly increased lean body mass and decreased fat mass related to the use of somatropin were reported in two meta-analyses of RCTs; however, inconsistent results were reported in two systematic reviews of RCTs and non-RCTs without data pooling. The impacts of the observed changes in body composition on clinical end points such as cardiovascular disease or mortality are uncertain.

Harms

The effect of somatropin therapy on mortality from systematic reviews was inconclusive as a result of scarce data. Results for glucose levels and blood pressure were inconsistent across two reviews of RCTs and non-RCTs.

Comparison of Somatropin Products Available in Canada

Somatropin products available in Canada for replacement of endogenous growth hormone in adults with GHD include Humatrope, Nutropin, Omnitrope, Saizen, and Genotropin. While there are differences in the manufacturing process, formulation components, administration methods, and recommended doses of these products, their pharmacokinetic profiles are only slightly different from each other. According to the clinical expert, these differences are unlikely to result in clinically important consequences. However, the differences in dosing and administration formats may add complexity when a patient is switched from one somatropin product to another.

Summary of Manufacturer-Submitted Placebo-Controlled Trials

The manufacturer's submission detailed six placebo-controlled RCTs of Genotropin, all of which were six months in duration. The only consistent benefit observed in these trials was improved body composition (i.e., increased lean body mass and reduced body fat). The clinical significance of the observed changes was uncertain. Positive effects on HRQoL, lipid profile, and bone mineral density were not consistently observed. The risks of adverse events were numerically higher in the Genotropin group compared with placebo. Common adverse events observed in the somatropin group included general disorders, peripheral swelling, and musculoskeletal disorders. All of the trials were small (N ranged from 20 to 52); hence, statistical power was likely limited for many outcomes. As well, all six trials excluded patients older than 60 years; hence, efficacy and safety data were not available for elderly patients.

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 adults with GHD. Similar clinical effectiveness for Genotropin versus comparators was assumed based on the results of one trial comparing Genotropin to Omnitrope in children with GHD. There were no published indirect comparisons of these agents. Based on CDR calculations using a confidential price of $[redacted] per milligram, the daily cost of the maximum dose of Genotropin ($[redacted]; 0.15 mg to 1.33 mg per day) is less than that of Humatrope ($49; 0.006 mg/kg to 0.0125 mg/kg per day), Nutropin ($82; 0.042 mg/kg to 0.175 mg/kg per week), and Omnitrope ($41; 0.15 mg to 1.33 mg per day), but higher than that of Saizen ($38; 0.005 mg/kg to 0.01 mg/kg per day).

Conclusions

There was no evidence to assess the relative efficacy and safety of Genotropin versus other somatropin products available in Canada for the treatment of adults with GHD. While all somatropin products have the same amino acid sequence as endogenous human GH and similar pharmacokinetic profiles, they differ somewhat with respect to manufacturing processes, dosage forms, excipients, dosing recommendations, and approved indications. Systematic reviews of somatropin products for the treatment of adult GHD indicate possible improvements in some dimensions of quality of life, exercise performance, lipid profile, and body composition compared with placebo or no treatment, although results were inconsistent across studies for some outcomes, and the clinical importance of the observed changes is uncertain. The only consistent benefit of Genotropin in the manufacturer-submitted placebo-controlled RCTs was improved body composition, but, once again, the effects were of uncertain clinical significance.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Growth hormone (GH) is produced by the pituitary gland and plays a role in achieving normal growth in children, and also plays a role in the regulation of protein, lipid and carbohydrate metabolism during both childhood and adult life.[1] Growth hormone deficiency (GHD) is observed in both children and adults. The majority of adult GHD (76%) cases are associated with pituitary tumours and subsequent surgery and radiotherapy. Other causes of this condition include non-pituitary tumours, head injury, and vascular lesions; it can also occur idiopathically.[2] Clinical manifestations in adults include decreased lean body and muscle mass, increased fat mass, reduced bone mineral density (BMD), lipid profile changes, and psychiatric symptoms.[3,4] Diagnosis of adult GHD is usually based on a medical history (childhood-onset GHD, hypothalamic–pituitary disease or surgery, cranial irradiation, or traumatic brain injury) and biochemical tests (GH stimulation tests).[2,4,5] In a European study, the prevalence of hypopituitarism was estimated at 29 to 45 per 100,000, and the incidence at 4.2 cases per 100,000 per year.[2] There are no data on prevalence or incidence of GHD in Canada.

1.2 Standards of Therapy

Once GHD is diagnosed, patients may receive replacement therapy with recombinant human growth hormone (also called somatropin) under the supervision of an endocrinologist.[2] The goals of replacement therapy are to correct the metabolic, functional, and psychological abnormalities associated with adult GHD.[4] For young adults with persistent GHD after attaining final height, it is recommended that GH treatment should be continued to achieve full somatic development, including the accrual of maximal bone and muscle mass. Elderly patients with proven GHD should be treated with GH, usually with lower doses (concordant with the physiological decrease in GH secretion).[2,4]

Each somatropin product is biosynthesized using recombinant DNA technology and has a sequence identical to that of human GH produced by the pituitary gland.[1] Many studies have suggested similarities in the clinical effectiveness and safety profile of the various available somatropin products.[6,7] Somatropin products that have been approved by Health Canada as replacement of endogenous growth hormone in adults with GHD (either adult or childhood-onset) include Humatrope, Nutropin, Omnitrope, Saizen, and Genotropin.[8,9]

Somatropin products are considered safe for both short and long-term use.[10,11] Doses of somatropin should be adjusted based on patients' age, weight, sex, risks of adverse effects, and insulin-like growth factor-1 (IGF-1) levels, and the use of somatropin should be monitored regularly.[2,5]

1.3 Drug

The Genotropin brand of somatropin was initially approved by Health Canada in 1998 for long-term therapy in patients with GHD, both adults and children.[12] At present, Genotropin is also indicated for short children born small for gestational age, Turner syndrome, and idiopathic short stature.[13] It is administered subcutaneously at a dose of 0.15 mg to 0.3 mg per day for adult GHD. The final dose should be individually increased as required with respect to age and gender to a maximum daily maintenance dose of 1.33 mg.[8]

Indication under review
Replacement of endogenous growth hormone in adults with growth hormone deficiency
Listing criteria requested by sponsor
List in a similar manner to other growth hormone products

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of recombinant somatropin (Genotropin) for the treatment of GHD in adults.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 1.

TABLE 1: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with GHD Subgroups of interest: adult-onset versus childhood-onset • in childhood-onset GHD, possible subgroups: isolated GHD versus structural pituitary disease (tumour, trauma, etc.)
Intervention	SC Genotropin 0.15 mg to 0.3 mg per day (final dose should be individually increased with respect to age and gender to a maximum daily maintenance dose of 1.33 mg)
Comparators	Other somatropin products approved in Canada: • Humatrope • Nutropin • Omnitrope • Saizen
Outcomes	**Key efficacy outcomes:** • Survival • Cardiovascular morbidity (myocardial infarction, stroke, congestive heart failure) • HRQoL by validated scales • Fracture rates • Fatigue, weakness, malaise, and exercise tolerance **Other efficacy outcomes:** • Lipid profile • BMD • Body composition (% body fat, % lean mass) **Harms outcomes:** Mortality, AEs, SAEs, WDAEs, harms of special interest (e.g., IGF-1 levels, glucose intolerance, neoplasm recurrence, fluid retention, hypertension, joint pain, carpal tunnel syndrome)
Study Design	Published and unpublished RCTs, with a study duration of at least six months

AE = adverse event; BMD = bone mineral density; GHD = growth hormone deficiency; HRQoL = health-related quality of life; IGF-1 = insulin-like growth factor-1; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse events.

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. 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 (CDEC) 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. APPENDIX 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

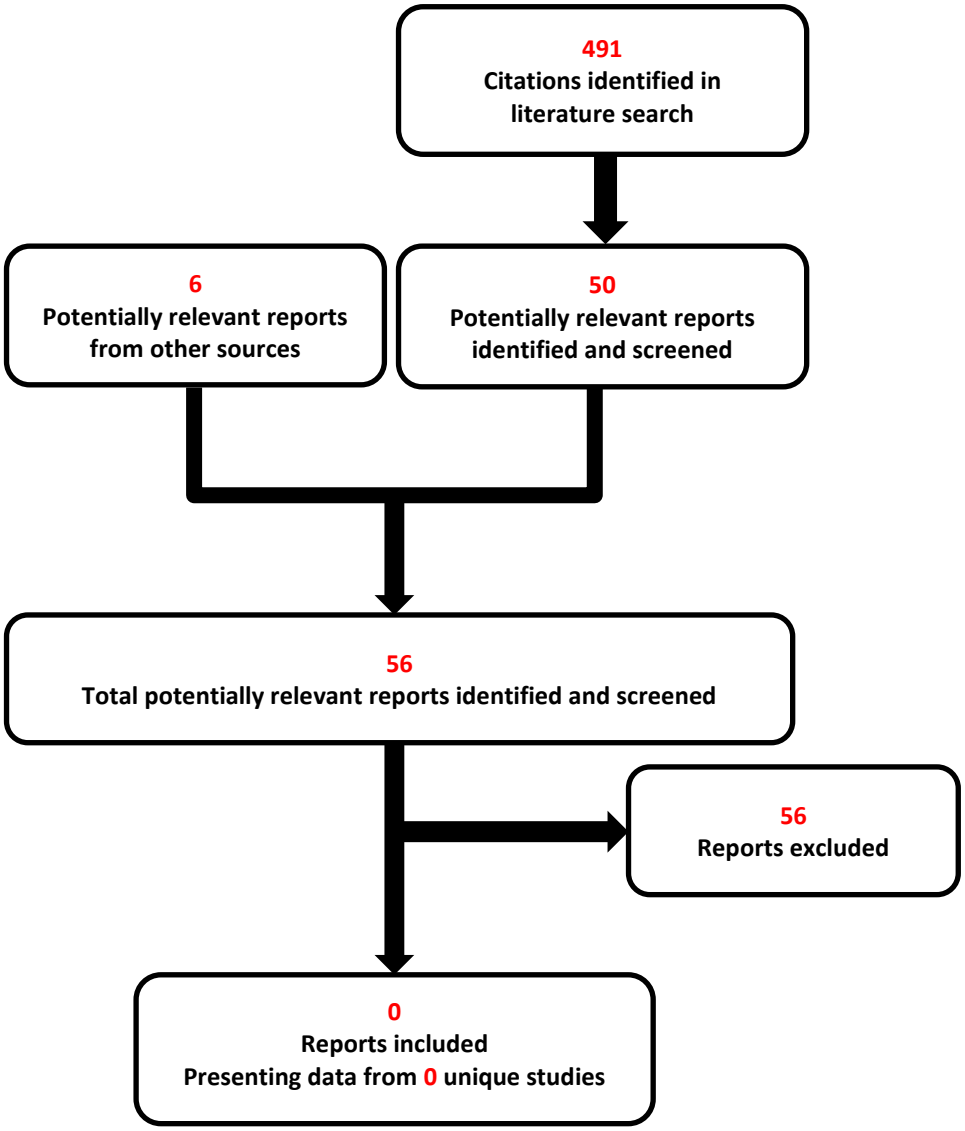
Two Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. No included studies were identified for this report. Excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

1.1 Findings from the Literature

No studies were identified from the literature for inclusion in the systematic review (Figure 1). A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

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



QUORUM = Quality of Reporting of Meta-analyses.

1.2 Included Studies

There were no studies that met the selection criteria of this review. Specifically, no randomized controlled trials (RCTs) comparing Genotropin with other somatropin agents for the treatment of GHD in adults were identified.

The manufacturer provided a series of double-blind, placebo-controlled RCTs that evaluated the efficacy and safety of Genotropin in adult patients with GHD; however, there were no active-controlled studies.[14]

Based on the lack of comparative evidence meeting the systematic review protocol, CDR, in consultation with the clinical expert contracted for the review, identified several key clinical issues to consider in the review of Genotropin.

1.3 Key Clinical Issues

3.3.1 Summary of Systematic Reviews on Somatropin for Adults with GHD

Without trials comparing Genotropin with other somatropin products in adults with GHD, we undertook a literature search to identify and describe systematic reviews that would provide information relevant to the evaluation of the efficacy and harms of somatropin in this population. Eight systematic reviews covering most of the clinically important outcomes in adults with GHD were identified.[15-22] The studies included in these reviews consisted of randomized and non-randomized trials, as well as observational studies. Five reviews included placebo-controlled RCTs exclusively.[17,19-22] One systematic review assessed the clinical effectiveness and safety in elderly patients (> 60 years) exclusively.[18] The number of included studies in each review ranged from 8 to 54. Use of somatropin was compared with no treatment or placebo, or a before–after treatment comparison was carried out in these studies. Outcome measures that were examined included health-related quality of life (HRQoL), body composition, lipid profile, BMD, exercise capacity, muscle strength and safety. Meta-analysis was performed in six of the eight systematic reviews.[16,17,19-22] All of the reviews treated the various somatropin products collectively without differentiating among them. Only one review specified the somatropin agents that were examined.[17] The systematic reviews included in this review are summarized in Table 2.

TABLE 2: SUMMARY OF SYSTEMATIC REVIEWS

Author, Year, Study Design	Key Inclusion Criteria, No. of Studies Included, Total Sample Size	Interventions or Comparators	Outcomes
Appelman-Dijkstra et al. (2013)[15] SR	Controlled or uncontrolled prospective studies with ≥ 5 years of somatropin therapy 23 prospective studies (11 controlled studies, 12 uncontrolled studies, 0 RCTs); sample size NR	Somatropin versus no treatment or healthy controls	QoL, body composition, lipid profile, BMD, muscle strength, safety
Xue et al. (2013)[16] MA	Studies reported BMD data on sites of spine or FN or TB, and with mean, SD, and SE of BMD 20 studies (RCTs, non-RCTs and SRs) with 936 patients: 18 studies on BMD of spine, 16 studies on BMD of FN, and 11 studies on BMD of TB	Before versus after somatropin therapy	BMD
Hazem et al. (2012)[17] SR/MA	RCTs comparing somatropin with placebo, with a study duration ≥ 3 months 54 RCTs in total, more than 3,400 patients	Somatropin versus placebo	QoL, body composition, safety
Kokshoorn et al. (2011)[18] SR	RCTs or non-randomized trials 11 studies in total, 534 patients	Somatropin versus placebo, or before versus after somatropin therapy	QoL, body composition, lipid profile, BMD
Widdowson and Gibney (2010)[20] MA	Placebo-controlled RCTs 8 RCTs, 231 patients	Somatropin versus placebo	Muscle strength
Rubeck et al. (2009)[19] MA	DB, placebo-controlled RCTs 15 RCTs, 306 patients	Somatropin versus placebo	Exercise capacity, muscle strength
Widdowson and Gibney (2008)[21] MA	Placebo-controlled RCTs 11 RCTs, 268 patients	Somatropin versus placebo	Exercise capacity
Maison et al. (2004)[22] MA	Double or single blinded placebo-controlled RCTs 37 RCTs, sample size NR	Somatropin versus placebo	Body composition, lipid profile, blood pressure

BMD = bone mineral density; DB = double blind; FN = femoral neck; MA = meta-analysis; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SR = systematic review; TB = total body.

a) Critical Appraisal of the Systematic Reviews

The methodological quality of the included systematic reviews was evaluated using the "assessment of multiple systematic reviews."[23]

Overall, the systematic reviews were conducted using acceptable methods to identify, extract, appraise, and summarize studies. Limitations included restriction to English-language publication only,[15,16] uncertainty as to whether grey literature searching was performed,[15,16,18-21] failure to assess the methodological quality of the included studies,[16,18,19] and lack of assessments for publication bias.[15,18,20,21] Conflict of interest and funding sources were reported in all but one review (Maison et al. 2004[22]). Results of the critical appraisal are summarized in Table 3 below.

TABLE 3: CRITICAL APPRAISAL OF SYSTEMATIC REVIEWS

Author, Year, Study Design	Strengths	Limitations
Appelman-Dijkstra et al. (2013)[15]	• Provided evidence on long-term treatment with somatropin • Literature search of multiple databases to September 2012 • Robust methods used for selection of studies, quality assessment, and data extraction • Conflict of interest was declared	• English language only • Publication bias was not assessed
Xue et al. (2013)[16]	• Literature search of multiple databases to December 2012 • Robust methods used for selection of studies, quality assessment, data extraction, and data synthesis • Publication bias was assessed • Conflict of interest was declared	• English language only • List of excluded studies was not provided • The scientific quality of the included studies was not assessed
Hazem et al. (2012)[17]	• Literature search of multiple databases as well as grey literature to April 2011 • Robust methods used for selection of studies, quality assessment, data extraction, and data synthesis • Publication bias was assessed • Conflict of interest was declared	• List of excluded studies was not provided
Kokshoorn et al. (2011)[18]	• Provided evidence of effectiveness and safety of somatropin in elderly patients • Conflict of interest was declared	• A search date was not reported • Did not indicate whether study selection or data extraction were conducted by independent reviewers • The scientific quality of the included studies was not assessed • Publication bias was not assessed
Widdowson and Gibney (2010)[20]	• Grey literature was searched to identify relevant studies • List of excluded studies was provided • Scientific quality of the included studies was assessed • Conflict of interest was declared	• Only one database was searched • One investigator conducted data extraction and quality assessment • Fixed-effect models were used for data analysis, but no justification provided • Publication bias was not assessed

Author, Year, Study Design	Strengths	Limitations
Rubeck et al. (2009)[19]	• Literature search in multiple databases • Robust methods used for selection of studies, data extraction and data synthesis • Publication bias was assessed • Conflict of interest was declared	• Not clear if quality of the included studies was assessed
Widdowson and Gibney (2008)[21]	• List of excluded studies was provided • Scientific quality of the included studies was assessed • Conflict of interest was declared	• Only one database was searched • One investigator conducted data extraction and quality assessment • Fixed-effect models were used for data analysis, but no justification provided • Publication bias was not assessed
Maison et al. (2004)[22]	• Literature search in multiple databases, and grey literature was searched for relevant studies • Robust methods used for selection of studies, data extraction and data synthesis • Publication bias was assessed • Quality of the included studies was assessed	• Conflict of interest was not reported

b) Summary of Key Characteristics of the Included Studies in the Systematic Reviews

The Appelman-Dijkstra et al., review[15] included 23 prospective studies, of which 11 had a control arm. No RCTs were identified by the review authors. The number of patients in the individual studies ranged from 10 to 13,983 (patient cohorts overlapped among some of these studies), and the treatment duration ranged from 4 to 15 years. Different doses of somatropin were used in each study, with a mean dose ranging from 0.3 mg to 0.8 mg per day. Dose titrations were determined according to body weight or IGF-1 levels according to the normal age and sex-related range. At baseline, patients ranged from 27 to 65 years of age. The vast majority of patients had adult-onset GHD.

The meta-analysis performed by Xue et al.[16] included 20 prospective studies evaluating effects of somatropin on BMD of total body, femoral neck, and spine. It is unclear how many RCTs were included. The numbers of patients in the individual studies ranged from 12 to 128, and treatment duration ranged from six months to 15 years. Different doses of somatropin were used in studies employing dosage adjustment according to body weight, body surface area, or IGF-1 levels. Age at baseline ranged from 17 to 74 years. Pooled standardized mean difference with 95% confidence interval (CI, using either fixed-effect or random-effect models, depending on heterogeneity among the included studies) were used to analyze the effects of somatropin therapy on BMD. The methodological quality of the included studies was not examined, although the authors stated that publication bias was not detected.

The meta-analysis by Hazem et al.[17] included the largest number of studies. Data on body composition and HRQoL from 54 placebo-controlled RCTs with more than 3,400 patients were synthesized. The numbers of patients in the individual studies ranged from 10 to 171, and the treatment duration ranged from 3 to 24 months. This was the only review that specified the type of somatropin products assessed. Genotropin, Humatrope, Nutropin and Norditropin were evaluated, and Genotropin was the most frequently investigated study drug. Different doses of somatropin were used in studies employing

dosage adjustment according to age, sex, body weight, body surface area, and IGF-1 levels. The dose of Genotropin in this review ranged from 0.4 mg to 1.8 mg per day (assuming 80 kg body weight). Age at baseline ranged from 18 to 79 years. Random-effect models were used to generate pooled relative risk (RR) or weighted mean difference (WMD); subgroup analyses were performed to seek explanations for inconsistency in results across trials. The methodological quality of the included studies was described as fair using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Significant publication biases for the outcomes of lean body mass and carpal tunnel syndrome were detected using funnel plots. The overall effects of somatropin versus placebo were reported, instead of individual effects of each somatropin product.

The Kokshoorn et al. review[18] included 11 prospective studies (two of them were placebo-controlled RCTs) enrolling patients older than 60 years. The numbers of elderly patients in the individual studies ranged from 10 to 135 (patient cohorts overlapped among some of these studies), and the treatment duration ranged from six months to 10 years. The two included RCTs recruited 34 and 31 patients, respectively, and the treatment durations ranged from 6 months to 12 months. Different doses of somatropin were used in each study, with a mean dose ranging from 0.16 mg to 0.5 mg per day. Doses titrations were based on clinical response, body weight, or IGF-1 levels. The methodological quality of the included studies was not assessed, nor was publication bias.

The meta-analysis by Rubeck et al.[19] included 15 double-blind placebo-controlled RCTs evaluating the clinical effects of somatropin on exercise capacity and muscle strength. The numbers of patients in the individual studies ranged from 9 to 38, and the treatment duration ranged from 3 to 12 months. The mean age at baseline ranged from 20 to 49 years. Different doses of somatropin were used in each study, with a mean dose ranging from 5 mcg/kg to 24 mcg/kg per day. The quality of the included studies was not reported, although the authors indicated that publication bias was unlikely in this review.

Widdowson and Gibney conducted a meta-analysis in 2008[21] to evaluate the effects of somatropin on exercise performance. It included 11 double-blind, placebo-controlled RCTs. The numbers of patients in the individual studies ranged from 10 to 55, and the treatment duration ranged from 6 to 18 months. Different doses of somatropin were used in each study, with a mean dose ranging from 3.3 mg to 15.7 mg per week. The mean age of patients at baseline ranged from 24 to 49 years. The methodological quality of the included studies was not reported, although the authors indicated that quality assessment had been performed. Data analysis was carried out using a fixed-effect model.

Widdowson and Gibney conducted another meta-analysis in 2010[20] to investigate the effects of somatropin on muscle strength in adults with GHD. Eight double-blind, placebo-controlled studies were included. The numbers of patients in the individual studies ranged from 14 to 35, and the treatment duration ranged from 3 to 12 months. The mean age of patients at baseline ranged from 29 to 49 years. Different doses of somatropin were used in each study, with a mean dose ranging from 3.3 mg to 13.3 mg per week. The methodological quality of the included studies was not reported, although the authors indicated that quality assessment had been performed. The methods for data synthesis were the same as the Widdowson and Gibney 2008 review.

Maison et al. conducted a meta-analysis of blinded placebo-controlled RCTs of somatropin on cardiovascular risk factors, such as blood pressure, blood glucose, lipid profile and body composition.[22] Thirty-seven trials (36 double-blind and 1 single-blind) were included. The numbers of patients in the individual studies ranged from 8 to 166, and the treatment duration ranged from 3 to 12 months.

The vast majority of the patients had adult-onset GHD. The mean age of patients at baseline ranged from 24 to 50 years. Different doses of somatropin were used in each study, with a mean dose ranging from 0.1 IU/kg to 0.56 IU/kg per week. The quality of the included studies was assessed based on study design, randomization method, blinding, and statistical methods. The authors indicated that the studies were generally of good quality, without providing further details, and that publication bias was unlikely. Global effect sizes for each outcome were calculated based on standardized effect sizes for each study. Random-effect models were adopted. The effects of the somatropin dose, treatment duration, percentage of patients with adult-onset GHD, and study design on overall estimates were assessed through stratification or meta-regression.

c) Summary of Efficacy Outcomes

Health-Related Quality of Life

HRQoL data were reported in two of the included systematic reviews.[15,17] The main findings are shown in Table 4.

Three questionnaires of HRQoL assessment were adopted in these reviews.

The Quality of Life–Assessment of Growth Hormone Deficiency in Adults (QoL–AGHDA) is a patient self-reported, condition-specific instrument for adults with GHD that can be used in clinical trials or for routine patient assessment. The questionnaire consists of 25 items with a Yes/No response format. A score of 1 is given to each "Yes" answer, and the total score is the sum of the individual scores for all 25 items. A higher total score represents poorer quality of life. The dimensions of the questionnaire are memory and concentration, friendships, social activities, mood, sleep, energy, work (paid or unpaid), confidence/self-esteem, family life, and expectations. The reliability, internal consistency, and construct validity of the QoL–AGHDA were described as good in a pharmaceutical company–sponsored study.[24] A minimal clinically important difference (MCID) for QoL–AGHDA was not identified in the literature.

The Nottingham Health Profile (NHP) is a self-administered, generic questionnaire that measures perceived health problems — social, physical, and mental. It consists of two parts. Part I (NHP I) has 38 statements measuring six dimensions of health: physical mobility (8 statements), sleep (5 statements), energy (3 statements), pain (8 statements), social isolation (5 statements) and emotional reactions (9 statements). Respondents are required to answer "Yes" or "No." The final score for each dimension is measured on a range from 0 to 100, with higher scores indicating poorer health. Part II of NHP (NHP II) provides a general estimate of social functioning perceived to be affected by individual health status. NHP II consists of one statement for each of the following seven areas: jobs around the home, paid employment, family relationships, sex life, holidays, hobbies/interests, and social life. Respondents are required to answer with "Yes" or "No."[25,26] The reliability and validity of NHP have not been evaluated in adult patients with GHD.

The Psychological General Well-Being Index (PGWBI) is a generic, self-administered questionnaire commonly used in adults with GHD to measure psychological well-being. PGWBI assesses six affective states (positive well-being, general health, depressed mood, self-control, and vitality) using 22 questions. The score for each question ranges from 0 to 5 (maximum total score is 110), or 1 to 6 in some studies (resulting in a total score of between 22 and 132). Higher scores indicate higher levels of psychological well-being. It is important to be aware of the different scoring algorithms, as they may affect the interpretation of the overall score.[27] The validity and reliability of this HRQoL questionnaire have been evaluated in adult- or childhood-onset GHD. An MCID for PGWBI was not identified in the literature.

In the Appelman-Dijkstra et al. review,[15] four non-RCTs with 2,197 patients reported HRQoL results. Treatment duration in these studies ranged from 4 to 10 years. Compared with no treatment or healthy controls, somatropin therapy was associated with improved overall psychological well-being, energy, and emotional reaction in one study (instrument not specified); another study reported higher energy levels with somatropin therapy (measured with NHP); the third study reported increase in vitality score (measured with PGWB); and the fourth study reported an improved QoL–AGHDA score in the first year of treatment, and a sustained improvement or regression to country-specific mean thereafter. The authors concluded that HRQoL improved during long-term somatropin therapy, particularly within the first year of treatment. However, no detailed HRQoL data were reported in this review.

The Hazem et al. review[17] also reported findings on HRQoL from 16 RCTs with treatment duration of 3 to 18 months. The HRQoL assessment questionnaires adopted included, but were not limited to, NHP, PGWBI, AGHDA, Beck Depression Index, General Health Questionnaire, General Well-being Questionnaire (GWBI) and SF-36. In 9 out of 16 studies, patients on somatropin therapy showed significant improvements from baseline in at least one subsection of general health, energy levels, the mood subsections, emotional reaction, and psychological distress. Five out of 16 studies reported no difference in HRQoL between somatropin and placebo. One study reported significant deterioration in physical activity, energy, and general health in the placebo group, but not in the somatropin group. However, two studies reported significant improvement in pain and social isolation with placebo compared with the somatropin group. The authors concluded that most trials of this review demonstrated improvement in HRQoL in somatropin-treated patients.

Presentation of HRQoL data was heterogeneous, and meta-analysis was not feasible in either review. In summary, some studies (RCTs and non-RCTs) have shown benefits of somatropin on certain dimensions of quality of life; however, benefits were not consistently observed.

TABLE 4: FINDINGS ON HRQOL FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	4 non-RCTs 2197	4 to 10 years	1/4 studies: increased overall psychological well-being, energy, emotional reaction 1/4 studies: increased energy levels with somatropin therapy (measured with NHP) 1/4 studies reported increased in vitality score (measured with PGWB). 1/4 studies: increased in first year, sustained or declined during longer follow-up.	QoL was improved during long-term somatropin therapy, especially in the first year of treatment.

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Hazem et al. (2012)[17]	16 RCTs No. of patients reported HRQoL data NR	3 to 18 months	9/16 studies reported significant improvement in at least one subsection of HRQoL assessment tool used. 5/16 studies reported no difference between somatropin and PL. 1/16 studies reported significant deterioration in HRQoL in PL, but not in somatropin. 2/16 studies reported significant improvement in pain in PL compared with somatropin.	Most trials demonstrated improvement in HRQoL in somatropin-treated patients.

HRQoL = health-related quality of life; NHP = Nottingham Health Profile; NR = not reported; PGWB = Psychological General Well-Being questionnaires; PL = placebo.

Exercise Capacity

Two meta-analyses reported summary results for the effect of somatropin therapy on exercise capacity (Table 5).[19,21] Significant benefits of somatropin replacement on exercise capacity were identified. In the Widdowson and Gibney 2008 review, the summary effect size for somatropin versus placebo was 0.34 for maximal oxygen uptake (VO_2 max), 0.4 for maximum power output, and 0.32 for overall combined variable set. All values were statistically significant. In the Rubeck et al. review, aerobic exercise capacity was measured as either VO_2 maximum, total work performed, or exercise time. A significant 8.9% increase in aerobic exercise capacity was observed with somatropin therapy versus placebo.

Muscle Strength

One systematic review and two meta-analyses reported results on muscle strength (Table 6). Summary effect sizes or WMDs between somatropin therapy and placebo were reported.[15,19,20] The Appelman-Dijkstra et al. review narratively reported its findings without data synthesis, and indicated that somatropin improved muscle strength during the first five years of treatment, but these effects were not sustained after prolonged follow-up. The Widdowson and Gibney 2010 review indicated that there was no statistically significant beneficial effect of somatropin therapy on muscle strength. The Rubeck et al. review failed to show a convincing effect of GH replacement on muscle strength.

TABLE 5: FINDINGS ON EXERCISE CAPACITY FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Widdowson and Gibney 2008[21]	11 RCTs 268	6 to 18 months	Effect size: 0.34 for VO_2 max (95% CI, 0.07 to 0.62) 0.4 for maximum power output (95% CI, 0.06 to 0.74) 0.32 for all variables combined (95% CI, 0.08 to 0.56)	Somatropin therapy improves exercise performance.
Rubeck et al. 2009[19]	15 RCTs 306	3 to 12 months	Aerobic exercise capacity increased significantly: 8.9 ± 0.8% ($P < 0.001$). VO_2 max: an increase of 0.17 ± 0.02 ($P < 0.001$)	Somatropin therapy was associated with significant positive effect on aerobic exercise capacity.

CI = confidence interval; RCT = randomized controlled trial; VO_2 max = maximal oxygen uptake; WMD = weighted mean difference.

TABLE 6: FINDINGS ON MUSCLE STRENGTH FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	5 non-RCTs 278	5 to 10 years	5 years of somatropin improved knee flexor and extensor and hand-grip strength; the effect was not sustained after 10 years. Somatropin did not affect muscle strength in elbow, shoulder, or hip.	Somatropin improved muscle strength during the first 5 years of treatment, but these effects were not sustained after prolonged follow-up.
Widdowson and Gibney (2010)[20]	8 RCTs 231	3 to 12 months Mean: 6.8 months	Isometric strength: Effect size: 0.02 (95% CI, –0.30 to 0.33, $P = 0.02$). Isokinetic strength: Effect size: 0 (95% CI, –0.45 to 0.45, $P = 0.15$).	No significant difference with somatropin on muscle strength over a mean duration of 6.8 months.
Rubeck et al. (2009)[19]	15 RCTs 306	3 to 12 months	WMD 3.24 (95% CI, –1.12 to 7.60, $P = 0.15$)	No significant difference between somatropin and placebo in muscle strength was observed.

CI = confidence interval; WMD = weighted mean difference.

Lipid Profile

Three systematic reviews and meta-analyses[15,18,22] examined the lipid profile in patients treated with somatropin (Table 7).

Inconsistent results were reported in the Appelman-Dijkstra et al. review, which assessed long-term lipid metabolism based on data from 10 studies involving 827 patients: 7 out of 10 studies reported favourable changes with somatropin therapy, while another 3 did not find changes in lipid profile after somatropin administration. No numerical data were provided in this review. The Kokshoorn et al. review presented consistent results favouring somatropin for total cholesterol (TC) and low-density lipoprotein (LDL) in elderly patients, but inconsistent results were reported for high-density lipoprotein (HDL). The Maison et al. review reported that somatropin significantly lowered TC and LDL. Overall, the effects of somatropin on lipid profile were inconsistent, although the systematic reviews were more likely to report lower TC and LDL with treatment.

TABLE 7: FINDINGS ON LIPID PROFILE FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	10 non-RCTs 827	5 to 10 years	7/10 studies reported reduced TC and LDL, and increased HDL with somatropin therapy. 3/10 studies did not detect a difference in TC, HDL and LDL between somatropin therapy and no somatropin therapy.	Somatropin replacement had ongoing beneficial effects on plasma lipids. (However, there was a lack of information on lipid-lowering medication.)
Kokshoorn et al. (2011)[18]	5 RCTs and non-RCTs 424	0.5 to 10 years	TC: reduced in 5 studies, by 4% to 8% LDL: reduced in 5 studies, by 11% to 16% HDL: increased in one RCT by 17%; no change in 3/5 studies	Somatropin decreased LDL levels.
Maison et al. (2004)[22]	TC: 15 RCTs, 616 LDL: 13 RCTs, 503	NR	TC: WMD = –0.34 mmol/L (SD 0.31) Effect size = –0.24 (95% CI, –0.39 to –0.08) LDL: WMD = –0.53 mmol/L (SD 0.29) Effect size = –0.35 (95% CI, –0.52 to –0.17)	Somatropin had beneficial effects on TC and LDL.

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; TC = total cholesterol; WMD = weighted mean difference.

Bone Mineral Density

Two systematic reviews reported effects of somatropin therapy on BMD. In the Appelman-Dijkstra et al. review,[15] results were inconsistent across the five non-RCTs that reported this outcome: BMD increased in three studies, while in another two studies, no differences were detected in BMD when somatropin was compared with no treatment, or a before–after treatment comparison was conducted. Two cases of bone fracture were reported in one study with 15 years' treatment duration (Table 8).

In the meta-analysis by Xue et al., the standardized mean differences in BMD were statistically significant between somatropin therapy and placebo or no treatment, on all three sites of interest (total body, spine, and femoral neck).

TABLE 8: FINDINGS ON BONE MINERAL DENSITY FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	5 non-RCTs 365	5 to 15 years	3/5 studies reported an increase in BMD. 2/5 study did not detect a difference in BMD for somatropin between treated and untreated patients. 1 study (without a control arm) reported fracture rate: 1 hip fracture and 1 symptomatic vertebral fracture.	Increase in BMD was observed within the first 5 years of treatment.
Xue et al. (2013)[16]	RCTs and non-RCTs on spine (18 studies), FN (16 studies) and TB (11 studies)	0.5 to 15 years	Association between GH therapy and BMD of spine: SMD = 0.54 (95% CI, 0.27 to 0.81), $P < 0.001$ Association between GH therapy and BMD of FN: SMD = 0.48 (95% CI, 0.19 to 0.76), $P = 0.001$ Association between GH therapy and BMD of TB: SMD = 0.24 (95% CI, 0.02 to 0.47), $P = 0.034$	Somatropin therapy may have beneficial influence on BMD in GHD adults.

BMD = bone mineral density; CI = confidence interval; FN = femoral neck; GH = growth hormone; GHD = growth hormone deficiency; RCT = randomized controlled trial; SMD = standardized mean difference; TB = total body.

Body Composition

Four reviews reported results regarding body composition.[15,17,18,22] In the Appelman-Dijkstra et al. review, most of the included studies reported increased lean body mass and decreased total body fat with somatropin therapy. The Hazem et al. review of RCTs reported statistically significant increases in lean body mass and decreased body fat mass after somatropin therapy. The Maison et al. review of RCTs also indicated favourable effects of somatropin on body composition. Inconsistent results for body

composition were reported in elderly patients in the Kokshoorn et al. review: somatropin had no impact on body composition in two trials, but had small effects on lean body mass and body fat in another four trials (Table 9).

TABLE 9: FINDINGS ON BODY COMPOSITION FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	11 non-RCTs 538	5 to 10 years	9/11 studies reported increasing LBM and decreasing total BF. 1/11 study did not detect a difference in LBM or BF between treated and untreated patients. 1/11 study reported decreasing visceral fat, but no difference in LBM, between treated and untreated patients.	Somatropin replacement had favourable effects on body composition: increase in LBM and decrease in total BF.
Hazem et al. (2012)[17]	54 RCTs More than 3,400	3 to 24 months	WMD for BF content: –2.56 kg (95%CI, –2.97 to –1.3) WMD for LBM: 1.38 kg (95% CI, 1.10 to 1.65)	Somatropin therapy decreased BF and increased LBM.
Kokshoorn et al. (2011)[18]	6 RCTs and non-RCTs 138	9 months to 10 years	2/6 studies found no effect of somatropin on body composition. 4/6 studies found significant increase in LBM by 2% to 5%, and significant decrease in BF by 7% to 10%.	Inconsistent effects of somatropin were found on body composition.
Maison et al. (2004)[22]	LBM: 19 RCTs, 947 BF: 13 RCTs, 697	NR	LBM: overall effect size = 0.45 (95% CI, 0.32 to 0.58) WMD = 2.74 kg (SD 2.67) BF: overall effect size = –0.62 (95% CI, –0.78 to –0.48 WMD = –3.05 kg (SD 3.29)	Somatropin therapy had beneficial effects on LBM and BF.

BF = body fat; CI = confidence interval; LBM = lean body mass; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; WMD = weighted mean difference.

d) Summary of Safety Outcomes

Mortality

Only one systematic review reported long-term (five to six years' study duration) mortality in adult patients with GHD.[15] Conflicting results were reported: according to data from three observational studies, increases in overall, cardiovascular or cerebrovascular-related, and infection-related mortality were observed in the study population after long-term somatropin therapy, compared with the general population; yet inconsistent findings were reported in other studies (Table 10). Data from one study showed that treatment with somatropin was not associated with a higher risk of malignancy-related death.

TABLE 10: FINDINGS ON MORTALITY FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	3 non-RCTs 16,501	5 to 10 years	Overall mortality: 1/3 studies reported an increase in overall mortality rate (especially in women) after long-term somatropin therapy versus general population; 2/3 studies reported no effect on overall mortality for somatropin. Malignancy mortality: All 3 studies reported that long-term somatropin had no effect on malignancy-related deaths. CVD or CVA-related mortality: 2/3 studies reported increasing CVD mortality (especially females) after long-term somatropin therapy; 1/3 studies reported that somatropin had no effect on CVD mortality, SMR = 2.36 (95% CI NR). Infection mortality: SMR = 4.97 (95% CI, 3.98 to 6.14) for somatropin-treated patients in 1 study	No firm conclusions on safety of long-term somatropin replacement can be drawn to scarce long-term data.

CI = confidence interval; CVA = cerebrovascular attack; CVD = cardiovascular disease; NR = not reported; RCT = randomized controlled trial; SMR = standardized mortality ratio.

Glucose Metabolism

Two systematic reviews reported the impacts of somatropin on glucose metabolism (Table 11). The Appelman-Dijkstra et al. review examined the long-term effects (5 to 10 years) of somatropin therapy on glucose metabolism. Elevated glucose levels in somatropin-treated patients were reported in some but not all studies in this review. The Maison et al. review reported statistically significantly elevated glucose levels with 2 to 18-month somatropin therapy compared with placebo.

TABLE 11: FINDINGS ON GLUCOSE METABOLISM FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	11 non-RCTs 847	5 to 10 years	7/11 studies did not detect effects of somatropin on glucose. 3/11 studies reported an increase in glucose. 1/11 study reported a transient increase in glucose levels only during the first year of somatropin therapy.	Somatropin replacement had moderate evidence for increase in mean glucose levels.
Maison et al. (2004)[22]	13 RCTs 511	NR	Overall effect on fasting glucose: 0.43 mmol/L (95% CI, 0.26 to 0.60) WMD in glucose between groups: 0.22 mmol/L (SD 0.14)	Somatropin therapy significantly increased plasma glucose.

CI = confidence interval; NR = not reported; RCT = randomized controlled trial; WMD = weighted mean difference.

Hypertension

Three systematic reviews assessed the impact of somatropin therapy on blood pressure in adults with GHD (Table 12).[15,18,22] The Appelman-Dijkstra et al. review reported that long-term treatment with somatropin had no effects on systolic blood pressure, while it may lower diastolic blood pressure. Effects of somatropin therapy were inconsistent in elderly patients enrolled in the included trials in the Kokshoorn et al. review. A statistically significant change in diastolic blood pressure was related to the use of somatropin in the Maison et al. review.

TABLE 12: FINDINGS ON BLOOD PRESSURE FROM SYSTEMATIC REVIEWS

Study	No. of Trials, Recruited Patients	Treatment Durations	Main Findings	Authors' Conclusions
Appelman-Dijkstra et al. (2013)[15]	4 135	5 to 10 years	4/4 studies: Somatropin had no effects on SBP. 3/4 studies: Somatropin had no effects on DBP. 1/4 studies: decrease in resting DBP	Somatropin replacement had no effect on SBP, and may lower DBP.
Kokshoorn et al. (2011)[18]	5 379	0.5 to 10 years	1/5 studies: did not affect BP 1/5 studies: transiently decreased BP 3/5 studies: decrease DBP only	No clear consistent effects of somatropin treatment on BP.
Maison et al. (2004)[22]	DBP: 10, 401 SBP: 9, 381	NR	DBP: Effect size = –0.25 (95% CI, –0.43 to –0.07) WMD = –1.80 mm Hg (SD 3.77) SBP: Effect size: NS for SBP WMD = 2.06 mm Hg (SD 5.34)	Somatropin therapy had beneficial effects on DBP.

CI = confidence interval; DBP = diastolic blood pressure; NR = not reported; NS = not significant; SBP = systolic blood pressure; SD = standard deviation; WMD = weighted mean difference.

Adverse events, serious adverse events, withdrawal due to adverse events and harms of special interest, such as change in IGF-1 levels and tumour occurrence, were not evaluated in any of the included systematic reviews.

In summary, eight systematic reviews assessing the effects of somatropin in adults with GHD were included in this review. All reviews except the Appelman-Dijkstra et al. review included RCTs, and five included placebo-controlled RCTs exclusively. Statistically significant improvements in exercise capacity were reported in somatropin-treated patients, compared with placebo. Conflicting results were reported for the outcomes of HRQoL, muscle strength, change in lipid profile, BMD, and body composition. Since an MCID is not available for the employed HRQoL assessment tools or other outcomes, and numerical estimates were rarely reported in the reviews, the clinical relevance of the observed improvements is unclear. Data for safety of somatropin were scarce and inconsistently reported.

3.3.2 Summary of All Somatropin Products Available in Canada

Given the large number of somatropin products already available in Canada, we sought to describe the similarities and differences among the available products.

The following somatropin products are presented in this section: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin. However, 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 current Canadian product monographs.[8,28-34]

a) Manufacturing Information, Formulations, Indications, and Dosing

As illustrated in Table 13, all products use recombinant DNA technology in *Escherichia coli* host cells except for Saizen, which is produced in mammalian-source host cells. Biological activity was not reported for all products, but it is most likely to be 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 GHD in children and adults, several of the products have additional indications for the treatment of Turner syndrome (Genotropin, Humatrope, Nutropin, and Saizen), 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 (Table 14). 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 13: DESCRIPTION OF RECOMBINANT GROWTH HORMONE PRODUCTS

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Genotropin	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human GH 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 0.2 to 2.0 mg per syringe: glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, and water for injection	Pediatric GHD, SGA, TS, ISS, and adult GHD

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Omnitrope	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human GH 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/1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, mannitol, benzyl alcohol, and water for injection	
				10 mg/1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, phenol, glycine, and water for injection	
Humatrope	Recombinant DNA technology Use *E. coli*, which is modified by addition of the human GH 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 glycerin	
Nutropin	Recombinant DNA technology Use *E. coli,* which is modified by addition of the	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	

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
	human GH gene			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	
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
				5 mg 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 GH 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

GH = growth hormone; GHD = growth hormone deficiency; 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 14: PHYSICAL DESCRIPTION AND DOSING OF RECOMBINANT GROWTH 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 0.24 mg/kg per week divided into 6 to 7 SC injections per week	0.15 mg per day to 0.3 mg per day to a max 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	5 mg 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 per 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 0.3mg/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	Up to 0.375 mg/kg per week divided into equal doses 3 to 7 injections per week by subcutaneous injection
	Solution	10 mg per 2 mL vial	IM or SC injection			
	Solution in pen cartridge	10 mg per 2 mL 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
					35 divided into 7 injections per week	
Saizen	Lyo powder	3.33 mg per vial and 5 mg per vial	Reconstitution and then IM or SC injection	0.2 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.

b) Pharmacokinetics and Pharmacodynamics

Although there are slight differences in the pharmacokinetic profiles of the different somatropin products based on the available information (Table 15), these differences do not appear to be significant and are not expected to result in important clinical consequences, according to the clinical expert consulted for this review. There is limited information on the pharmacodynamic properties of the other somatropin products in Canada. According to information available, Omnitrope appears to be very similar in its pharmacodynamic properties to Genotropin (Table 16).

TABLE 15: PHARMACOKINETIC PROFILE OF RECOMBINANT HUMAN GROWTH HORMONE 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 (SD 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	4.0 to 4.5	3			

AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration of drug; IM = intramuscular; lyo = lyophilized; NR = not reported; SC = subcutaneous; SD = standard deviation; 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 16: PHARMACODYNAMIC PROFILE OF RECOMBINANT HUMAN GROWTH HORMONE PRODUCTS

Pharmacodynamics IGF-1	AUEC (h-mcg/L ± SD)	E_{max} (mcg/L ± SD)	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; 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).

3.3.3 Placebo-Controlled Studies for Genotropin (Submitted by Manufacturer)

There were no active-controlled RCTs available to evaluate the relative clinical benefits and harms of Genotropin compared with other somatropin products in adults with GHD. The manufacturer submitted a series of placebo-controlled RCTs. The purpose of this section is to summarize evidence of clinical efficacy and safety of Genotropin in the study population versus placebo. Six double-blind RCTs comparing Genotropin and placebo are described.

Study design and key selection criteria of these trials are presented in Table 17. All trials used the same inclusion/exclusion criteria. Adult patients who had been diagnosed with GHD for at least two years (confirmed with GH stimulation tests) were recruited. Doses of Genotropin were consistent with approved doses for adult GHD. HRQoL, condition-relevant biomarkers, and safety were examined. All trials had a 6-month double-blind treatment period. After the initial 6-month double-blind phase, the trials were continued as open-label studies for another 6 to 30 months, when all patients in both groups received Genotropin.

TABLE 17: SUMMARY OF TRIAL CHARACTERISTICS

Study	Study Design	Key Inclusion and Exclusion Criteria	Intervention or Comparator[a]	Outcome
CTN 92-8142-011[35]	DB RCT, 6-month	GHD > 24 months; stimulated maximum peak GH response < 5 µg/L; on stable replacement therapy; age 20 to 60 years	Genotropin 0.125 IU/kg per week during the first month, thereafter 0.25 IU/kg per week Placebo	QoL, body composition, lipid profile; BMD, IGF-1, safety
TRN 91-001[36]			Genotropin 0.25 IU/kg per week (0.125 IU/kg per week during the first and sixth month) Placebo	QoL, exercise capacity, body composition, lipid profile, BMD, IGF-1, and safety
TRN 91-081-01[37]			Genotropin 0.125 IU/kg per week during the first month, thereafter 0.25 IU/kg per week Placebo	QoL, body composition, BMD, lipid profile, immune function, IGF-1, and safety
TRN 91-081-02[38]				Body composition, BMD, cardiovascular function, serum lipids, coagulation factors, IGF-1, insulin sensitivity, HRQoL, and safety
TRN 91-131-04[39]				Body composition, BMD, IGF-1 and IGFBP-3, bone mineral content, HRQoL, and safety
TRN 91-131-08[40]				Body composition, IGF-1, BMD, muscle strength, exercise tolerance, HRQoL, and safety

BMD = bone mineral density; DB = double blind; GH = growth hormone; GHD = growth hormone deficiency; HRQoL = health-related quality of life; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor binding protein-3; QoL = quality of life; RCT = randomized controlled trial.

[a] For the periods when compared with placebo.

The numbers of patients enrolled in these trials ranged from 20 to 52. Baseline patient characteristics were similar between treatment groups (Table 18).

TABLE 18: BASELINE PATIENT CHARACTERISTICS

Study	Treatment Groups	Age (Years, Mean ± SD)	Sex (M/F)	Laboratory Values			
				BMD (g/cm^2, Mean ± SD)	Lipid Profile (mmol/L, Mean ± SD)	Body Composition (kg, Mean ± SD)	IGF-1 (Mean ± SD)
CTN 92-8142-011[35]	Genotropin N = 10	46.8 ± 7.9	6/4	Total: 1.14 ± 0.11 Lumbar: NR	TC: 7.1 ± 0.8 HDL: NR LDL: NR	LBM: 47.3 ± 12.2 BF: 31.0 ± 9.6	100 ± 59 ng/mL
	PL N = 10	39.6 ± 12.2	8/2	Total: 1.16 ± 0.09 Lumbar: NR	TC: 6.1 ± 1.0 HDL: NR LDL: NR	LBM: 48.3 ± 15.6 BF: 26.0 ± 9.4	95 ± 55 ng/mL
TRN 91-001[36]	Genotropin N = 10	40.7 ± 9.1	5/5	Total: 1.09 ± 0.14 Lumbar (dorsal): 1.06 ± 0.21	TC: 4.69 ± 0.77 HDL: 1.05 ± 0.28 LDL: 3.31 ± 0.81	LBM: 51.8 ± 12.6 BF: 25.4 ± 13.6	47 ± 25 mcg/L
	PL N = 10	39.8 ± 6.0	6/4	Total: 1.09 ± 0.16 Lumbar (dorsal): 1.13 ± 0.20	TC: 5.29 ± 0.81 HDL: 1.17 ± 0.30 LDL: 3.72 ± 0.71	LBM: 53.5 ± 10.1 BF: 26.3 ± 8.9	37 ± 22 mcg/L
TRN 91-081-01[37]	Genotropin N = 12	49	5/7	Total: 1.20 Lumbar (dorsal): 1.18	TC: 5.4 HDL: 1.1 LDL: NR	LBM: 53.6 BF: 23.3	56 ng/mL
	PL N = 13	49	11/2	Total: 1.23 Lumbar (dorsal): 1.19	TC: 6.2 HDL: 1.1 LDL: NR	LBM: 63.6 BF: 17.4	67 ng/mL
TRN 91-081-02[38]	Genotropin N = 12	Median (range): 43 (24 to 60)	6/6	Total: 1.12 (0.99 - 1.20)[a] Lumbar: 1.18 (0.94 - 1.26)[a]	TC: 5.7 (4.9 - 6.6)[a] HDL: 1.1 (0.9 - 1.5)[a] Trig: 1.1 (0.8 - 1.7)[a]	LBM: 46.6 (36.7 - 59.6)[a] BF: 26.4 (21.1 - 27.8)[a]	24 (20 - 60)[a]

Study	Treatment Groups	Age (Years, Mean ± SD)	Sex (M/F)	Laboratory Values			
				BMD (g/cm^2, Mean ± SD)	Lipid Profile (mmol/L, Mean ± SD)	Body Composition (kg, Mean ± SD)	IGF-1 (Mean ± SD)
	PL N = 11	Median (range): 45 (23 to 60)	10/1	Total: 1.13 (0.93 - 1.21)[a] Lumbar: 1.07 (0.86 - 1.20)[a]	TC: 5.4 (5.05 - 5.9)[a] HDL: 1.0 (0.8 - 1.0)[a] Trig: 1.6 (1.1 - 3.6)[a]	LBM: 46.6 (37.5 - 58.1)[a] BF: 22.2 (14.6 - 27.5)[a]	67 (41 - 115)[a]
TRN 91-131-04[39]	Genotropin N = 14	38.0 ± 11.6 (range 23.8 to 55.4)	7/7	Total: 1.161 ± 0.103 Lumbar: 1.12 ± 0.13	NR	LBM: 45.8 ± 12.2 BF: 26.8 ± 11.9	IGF-1-SDS: –1.27 ± 1.75 IGF-1, mcg/L: 142 ± 72
	PL N = 18	40.9 ± 11.4 (range 21.2 to 59.5)	9/9	Total: 1.181 ± 0.117 Lumbar: 1.13 ± 0.15		LBM: 48.5 ± 12.1 BF: 27.4 ± 7.2	IGF-1-SDS: –1.94 ± 1.81 IGF-1, mcg/L: 109 ± 48
TRN 91-131-08[40]	Genotropin N = 27	40 ± 11 (range 21 to 60)	15/12	Total: 1.153 ± 0.091 Lumbar: 1.00 ± 0.15	NR	LBM: 52.483 ± 12.458 BF: 23.370 ± 10.330	IGF-1-SDS: –2 ± 2 IGF-1: 109 ± 56
	PL N = 25	39 ± 11 (range 22 to 60)	13/12	Total: 1.159 ± 0.116 Lumbar: 0.96 ± 0.18		LBM: 48.513 ± 13.313 BF: 22.159 ± 8.408	IGF-1-SDS: –3 ± 2 IGF-1: 84 ± 48

BF = body fat; BMD = bone mineral density; F = female; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; LBM = lean body mass; LDL = low-density lipoprotein; M = male; NR = not reported; PL = placebo; SD = standard deviation; SDS = standard deviation score; TC = total cholesterol.
[a] Median values (1st - 3rd quartile)

a) Efficacy Outcomes

Survival

No data were reported on survival.

Cardiovascular Morbidity
None of the six trials reported cardiovascular morbidity.

Fracture Rates
No data were reported on fracture rates.

Fatigue/Exercise Tolerance
Physical exercise capacity (measured by maximum load, systolic blood pressure, pulse, and oxygen consumption) was assessed in TRN 91-001. No statistically significant changes or differences in this outcome during the six-month double-blind period were reported.

Health-Related Quality of Life
After six months, improvements in HRQoL were observed in both Genotropin and placebo arms. Greater improvements in energy (measured with NHP) with Genotropin therapy were reported in two studies, while greater improvements with placebo were reported in another two studies. For trials using PGWB for HRQoL assessment, changes in HRQoL were comparable between treatment groups (Table 19).

TABLE 19: HEALTH-RELATED QUALITY OF LIFE (EFFICACY POPULATION)

Study	Treatment Groups	NHP (Positive Score Indicates Impaired HRQoL)	PGWB (Positive Score Indicates Better HRQoL)
CTN 92-8142-011[35]	Genotropin N = 10	Change from baseline: Energy: –13 Pain: 0 Emotional reaction: –10 Sleep: +2 Social isolation: –4 Physical mobility: –3	NR
	PL N = 10	Change from baseline: Energy: –14 Pain: –1 Emotional reaction: –15 Sleep: +5 Social isolation: –10 Physical mobility: –4	
	Between-group comparison	Improvement in health status was seen in both groups.	
TRN 91-001[36]	Genotropin N = 10	Change from baseline: Energy: –25.9 Pain: 0 Emotional reaction: –3.7 Sleep: –6.7 Social isolation: –4.4 Physical mobility: 4.7	Change from baseline: Anxiety: 3.1 Depressed mood: 0.5 General health: –0.1 Positive well-being: 1.1 Self-control: 0.6 Vitality: 2.7 PGWBI: 7.9
	PL N = 10	Change from baseline: Energy: –3.3 Pain: –3.8 Emotional reaction: –2.2 Sleep: 0 Social isolation: –14.0	Change from baseline: Anxiety: 1.5 Depressed mood: 0.8 General health: 1.4 Positive well-being: 1.5 Self-control: 0.5

Study	Treatment Groups	NHP (Positive Score Indicates Impaired HRQoL)	PGWB (Positive Score Indicates Better HRQoL)
		Physical mobility: –1.3	Vitality: 2.1 PGWBI: 7.8
	Between-group comparison	Improvement in energy was observed in the somatropin group. *P* value NR	Changes in HRQoL scores were comparable between groups. *P* value NR
TRN 91-081-01[37]	Genotropin N = 12	Change from baseline: Energy: –19.4 Pain: 2.3 Emotional reaction: –10.2 Sleep: –3.3 Social isolation: –6.7 Physical mobility: 2.1	Change from baseline: Anxiety: 1.8 Depression: 1.6 Positive well-being: 2.8 Self-control: 1 General health: –0.3 Vitality: 3.1
	PL N = 13	Change from baseline: Energy: 0 Pain: 0 Emotional reaction: –1.2 Sleep: –4.6 Social isolation: –3.1 Physical mobility: 1.0	Change from baseline: Anxiety: 0.8 Depression: 0.6 Positive well-being: 1.1 Self-control: 0.2 General health: 0 Vitality: 0.5
	Between-group comparison	Greater improvements were seen in energy and emotional reaction with Genotropin. *P* value NR	Changes in HRQoL scores were comparable between groups. *P* value NR
TRN 91-081-02[38]	Genotropin N = 11	Change from baseline: Energy: 6.7 Pain: 2.3 Emotional reaction: –3.0 Sleep: 1.8 Social isolation: –5.5 Physical mobility: 5.7	Change from baseline: Anxiety: –0.2 Depression: –0.7 Positive well-being: 1.7 Self-control: –0.2 General health: –0.5 Vitality: 2.8 PGWB, total score: 2.0
	PL N = 10	Change from baseline: Energy: –21.2 Pain: –1.3 Emotional reaction: –7.1 Sleep: –7.3 Social isolation: 7.3 Physical mobility: –2.3	Change from baseline: Anxiety: 0.7 Depression: 0.1 Positive well-being: 0.2 Self-control: 0.7 General health: 0.2 Vitality: 1.5 PGWB, total score: 3.4
	Between-group comparison	Greater improvements were seen in energy with placebo. *P* value NR	Changes in HRQoL scores were comparable between groups. *P* value NR
TRN 91-131-04[39]	Genotropin N = 12	Change from baseline: Energy: –12.9 Pain: –0.7 Emotional reaction: –6.2 Sleep: –1.3 Social isolation: –6.4 Physical mobility: 0	NR

Study	Treatment Groups	NHP (Positive Score Indicates Impaired HRQoL)	PGWB (Positive Score Indicates Better HRQoL)
	PL N = 17	Change from baseline: Energy: –20.0 Pain: –0.7 Emotional reaction: –7.1 Sleep: –0.8 Social isolation: –2.1 Physical mobility: –4.5	
	Between-group comparison	Greater improvements were seen in energy with placebo, p value NR	
TRN 91-131-08[40]	Genotropin N = 23	Change from baseline: Emotional: –5.60 (49) Energy: –19.03 (31.88) Pain: 0.83 (4.90) Physical mobility: –4.86 (14.34) Sleep: –6.68 (21.65) Social isolation: –3.61 (10.33)	NR
	PL N = 23	Change from baseline: Emotional: –8.94 (22.86) Energy: –15.23 (31.44) Pain: 0.39 (12.90) Physical mobility: 0.39 (6.01) Sleep: –5.96 (12.39) Social isolation: –2.99 (15.16)	
	Between-group comparison	Greater improvement in physical mobility with Genotropin. *P* value NR	

NHP = Nottingham Health Profile; NR = not reported; PGWBI = Psychological General Well-Being Index; PL = placebo.

Lipid Profile

There were no statistically significant differences in levels of TC, HDL or LDL between Genotropin and placebo after six months' treatment (Table 20).

Bone Mineral Density

Most of the placebo-controlled trials reported statistically non-significant differences between Genotropin and placebo in changes in BMD from baseline to six months. Study TRN 91-081-02[38] reported a significant difference in lumbar BMD at six months between the treatment groups (Genotropin: 1.16 g/cm^2 versus placebo 1.07 g/cm^2, *P* = 0.015). On the other hand, Study TRN 91-131-04 reported a significant difference in total body BMD in favour of placebo at six months (Genotropin: 1.14/cm^2 versus placebo: 1.19/cm^2, *P* = 0.007) (Table 20).

Body Composition

All but two trials (CTN 92-8142-011[35] and TRN 91-081-01[37]) indicated that treatment with Genotropin was associated with significant decreases in body fat and significant increases in lean body mass compared with placebo at the end of the double-blind treatment phase (Table 20).

TABLE 20: LIPID PROFILE, BMD, AND BODY COMPOSITION

Study	Treatment Groups	Lipid Profile (mmol/L, Mean ± SD)			BMD (g/cm^2, Mean ± SD)		Body Composition (kg , Mean ± SD)	
		TC	HDL	LDL	Total Body	Lumbar	BF	LBM
CTN 92-8142-011[35]	Genotropin N = 10	6 month: 6.8 ± 1.3	NR	NR	6 month: 1.12	NR	Change:[a] –0.7 ± 1.4	Change: 0.2 ± 2.2
	PL N = 10	6 month: 6.5 ± 1.5			6 month: 0.10		Change: 1.2 ± 4.3	Change: 0 ± 1.4
	Between-group comparison	NS			NS		*P* = 0.046	NS
TRN 91-001[36]	Genotropin N = 10	Change: 0.05 ± 0.68	Change: 0.03 ± 0.23	Change: –0.07 ± 0.60	Change: –1.24 ± 2.29	Change (dorsal): –1.97 ± 4.63	Change: –3.0 ± 2.8	Change: 2.8 ± 1.3
	PL N = 10	Change: –0.04 ± 0.72	Change: –0.03 ± 0.18	Change: 0.08 ± 0.63	Change: 0.48 ± 1.30	Change (dorsal): –1.86 ± 2.74	Change: 0.9 ± 2.4	Change: 0.5 ± 3.3
	Between-group comparison	NS	NS	NS	NS	NS	*P* = 0.007	*P* = 0.028
TRN 91-081-01[37]	Genotropin N = 12	6 month: 5.4	6 month: 1.2	NR	6 month: 1.22	6 month: 1.20	Change: –3.9	Change: +1.9
	PL N = 13	6 month: 5.9	6 month: 1.1		6 month: 1.25	6 month: 1.21	Change: –0.4	Change: +0.9
	Between-group comparison	NS	*P* = 0.02		NS	NS	*P* = 0.007	NS
TRN 91-081-02[38]	Genotropin N = 12	5.9 (4.6 - 6.4)[a]	1.1 (1.0 - 1.3)[a]	NR	6 month: 1.09 (0.97 - 1.17)[a]	6 month: 1.16 (0.92 - 1.23)[a]	DEXA technique: –1.4 4-comp.model technique: 1.9	DEXA technique: 1.8 4-comp.model technique: –1.7
	PL N = 11	5.6 (5.4 - 5.9)[a]	0.9 (0.7 - 1.0)[a]	NR	6-month: 1.13 (0.95 - 1.20)[a]	6-month: 1.07 (0.71 - 1.21)[a]	DEXA technique: 1.1 4-comp.model technique: 4.9	DEXA technique: 0.5 4-comp.model technique: –5.0

Study	Treatment Groups	Lipid Profile (mmol/L, Mean ± SD)			BMD (g/cm^2, Mean ± SD)		Body Composition (kg , Mean ± SD)	
		TC	HDL	LDL	Total Body	Lumbar	BF	LBM
	Between-group comparison	NS	NS		NS	*P* = 0.015	DEXA *P* = 0.002 4-comp.model NS	DEXA *P* = 0.034 4-comp.model NS
TRN 91-131-04[39]	Genotropin N = 12	NR			6 month: 1.14 ± 0.11	6 month: 1.11 ± 0.13	26.0 ± 13.1	47.5 ± 12.8
	PL N = 17				6 month: 1.19 ± 0.12	6 month: 1.13 ± 0.15	28.9 ± 7.8	48.1 ± 11.9
	Between-group comparison				*P* = 0.007	NS	*P* < 0.001	*P* = 0.023
TRN 91-131-08[40]	Genotropin N = 17	NR			–0.18 ± 2.43[c]	0.54 ± 2.79[c]	Change: –2.66 ± 2.19[b]	Change: 2.39 ± 2.16[b]
	PL N = 16				0.74 ± 0.82[c]	0.84 ± 3.04[c]	Change: 0.47 ± 2.16[b]	Change: 0.35 ± 2.14[b]
	Between-group comparison				NS	NS	*P* < 0.001	*P* = 0.009

BF = body fat; DEXA = dual-energy X-ray absorptiometry; HDL = high-density lipoprotein; LBM = lean body mass; LDL = low-density lipoprotein; NR = not reported; NS = not significant; PL = placebo; TC = total cholesterol.
[a] Median values (1st - 3rd quartile)
[b] Absolute change from baseline.
[c] Relative change from 0 to 6 months (%).

b) Safety

Adverse events and serious adverse events were reported more often in the Genotropin group than in the placebo group, except in one trial (CTN92-8142-011[35]). Common adverse events observed in the Genotropin group included gastrointestinal disorders, musculoskeletal system events, nervous system disorders, and peripheral swelling; whereas, general disorders, gastrointestinal disorders, peripheral swelling, and headache were frequently reported in the placebo group (Table 21). There were no reports of deaths.

TABLE 21: SAFETY (SAFETY POPULATION)

Study	Treatment groups	AEs	SAEs	WDAEs	Death
CTN 92-8142-011[35]	Genotropin N = 9	23 events Common AEs: Respiratory tract infections (3) GI disorders (3)	0	0	0
	PL N = 9	32 events Common AEs: GI disorders (6) Psychiatric disorders (4)	3 events Reasons: Worsening headache (1) Vaginal bleeding (1) Infected hematoma (1)	0	0
TRN 91-001[36]	Genotropin N = 10	21 events Common AEs: Arthralgia (8) Stiffness of extremities (4)	1 patient Acute tonsillitis with high fever	0	0
	PL N = 10	1 event Upper respiratory tract infection (1)	1 patient Gastroenteritis leading to cortisol deficiency	0	0
TRN 91-081-01[37]	Genotropin N = 12	32 events Common AEs: Swollen fingers/feet Paresthesias/numbness in fingers	3 patients (unclear whether these SAEs occurred during the DB period)	0	0
	PL N = 13	21 events Common AEs: Swollen fingers/feet Paresthesias/numbness in fingers	1 patient (unclear whether this SAE occurred during the DB period)	0	0
TRN 91-081-02[38]	Genotropin N = 12	36 events Common AEs: Muskuloskeletal system disorders: 8 Respiratory system disorders: 4 General disorders: 10	2 events	0	0
	PL N = 11	2 events Psychiatric disorders: 1 Resistance mechanism disorder: 1	0	0	0
TRN 91-131-04[39]	Genotropin N = 14	64 events Common AEs: Skin and appendages: 5	3 events	0	0

Study	Treatment groups	AEs	SAEs	WDAEs	Death
		Musculoskeletal system: 7 Central and peripheral nervous system: 10 Body as a whole — general: 10			
	PL N = 18	44 events Common adverse reactions: GI system: 5 Respiratory system: 5 Body as a whole — general: 13	1 event	0	0
TRN 91-131-08[40]	Genotropin N = 27	125 events Common AEs: Peripheral swelling: 18 Pain in the extremities: 11 Headache: 8	2 events	0	0
	PL N = 25	57 events Common AEs: Peripheral swelling: 4 Headache: 5	0	0	0

AE = adverse event; DB = double blind; GI = gastrointestinal; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Insulin-like growth factor-1

All trials reported statistically significant increases in IGF-1 levels in the Genotropin-treated patients, compared with those treated with placebo, at the end of six months (Table 22).

Glucose

All but one trial (TRN 91-131-08[40]) reported elevated glucose levels in patients treated with Genotropin, compared with placebo; however, the between-group differences were statistically significant in only one trial (CTN 92-8142-011[35]) (Table 22).

TABLE 22: INSULIN-LIKE GROWTH FACTOR-1 AND GLUCOSE

Study	Treatment groups	IGF-1 (Mean ± SD)	Glucose (mmol/L, Mean ± SD)
CTN 92-8142-011[35]	Genotropin N = 10	6 month: 259 ± 144 ng/mL	Change:[a] +0.3
	PL N = 10	6 month: 103 ± 71 ng/mL	Change: –0.2
	Between-group comparison	*P* = 0.0007	*P* = 0.026
TRN 91-001[36]	Genotropin N = 10	Change: 205 ± 123 mcg/L	Change: 0.6 ± 0.6
	PL N = 10	Change: –1 ± 9 mcg/L	Change: 0.2 ± 0.3
	Between-group comparison	*P* < 0.001	NS
TRN 91-081-01[37]	Genotropin N = 12	6 month: 202 ng/mL	6 month: 4.1
	PL N = 13	6 month: 70 ng/mL	6 month: 3.6
	Between-group comparison	*P* < 0.001	NS
TRN 91-081-02[38]	Genotropin N = 12	162 (79 - 223)[b]	Total glucose used, g: 55 (28 - 74)[b] M-value glucose, mg/kg per minute (last 60 minutes): 7.7 (3.7 - 8.7)[b] Beta-glucose (fasting), mmol/L: 4.3 (4.0 - 4.6)[b]
	PL N = 11	72 (32 - 117)[b]	Total glucose used, g: 45 (36 - 70)[b] M-value glucose, mg/kg per minute (last 60 minutes): 7.3 (3.5 - 9.8)[b] beta-glucose (fasting), mmol/L: 4.2 (3.8 - 4.69)[b]
	Between-group comparison	*P* = 0.002	NS
TRN 91-131-04[39]	Genotropin N = 12	389 ± 127	beta-glucose (fasting), mmol/L: 5.2 ± 1.0
	PL N = 17	129 ± 68	beta-Glucose (fasting), mmol/L: 4.9 ± 0.5
	Between-group comparison	*P* < 0.001	NR
TRN 91-131-08[40]	Genotropin N = 27	Change: 210 ± 148	Change: beta-glucose mmol/L: 0.1 ± 0.6
	PL N = 25	Change: –3 ± 26	Change: beta-glucose mmol/L: 0.1 ± 0.4
	Between-group comparison	*P* < 0.001	NS

IGF-1 = insulin-like growth factor-1; M-value = the calculated glucose infusion rate; NR = not reported; NS = not significant; PL = placebo.

[a] All changes indicated are from baseline

[b] Median values (1st - 3rd quartile)

Limitations of these studies include:

- There was a lack of evidence on some clinically important outcomes that were indicated in the protocol of this review, such as cardiovascular morbidity, fracture rates, and exercise tolerance.
- The studies enrolled small numbers of patients. The statistical methods section of the clinical study reports[35-39,41] indicated that 10 patients in each group should be sufficient to detect a difference equivalent to an 8.3% increase in lean body mass. However, it is likely that there was insufficient statistical power for other clinically important outcomes.
- The short duration (six months) of these double-blind RCTs does not allow for assessment of long-term efficacy or safety.
- The generalizability of these studies to elderly patients is uncertain since all studies enrolled patients between 20 and 60 years of age.

In summary, improvements in body composition (increased lean body mass, reduced body fat) were observed with Genotropin compared with placebo in the reviewed trials; however, no evidence was found to determine whether these changes are clinically significant. No consistent benefits of Genotropin on HRQoL, lipid profile, or BMD were observed. Genotropin was associated with a higher risk of adverse events and serious adverse events. Limitations of the trials were their relatively short duration and small sample sizes.

4. DISCUSSION

1.4 Summary of Available Evidence

No RCTs comparing Genotropin with other somatropin products in adults with GHD were identified in this review, nor were there indirect comparisons of these products. The following information was reviewed in order to provide context for the use of Genotropin in adults with GHD: a summary of systematic reviews of treatments for adult GHD; a summary of all somatropin products available in Canada; and a summary of placebo-controlled studies of Genotropin in adult patients with GHD.

1.5 Interpretation of Results

Some of the potential benefits of somatropin in adults with GHD include improved HRQoL, improved exercise capacity, increased BMD, enhanced body composition, and slightly decreased blood pressure.[5] Patient group input received by CDR also suggested that treatment with somatropin was felt to improve mental health, social relationships, and energy level. Two systematic reviews reviewed by CDR found benefits on some dimensions of HRQoL with somatropin; however, results were inconsistent across studies. As well, the clinical relevance of any observed benefits was uncertain since numerical results were not presented and MCIDs were not available. Two meta-analyses of RCTs on exercise capacity suggested statistically significant improvements in exercise capacity for patients receiving somatropin therapy compared with placebo. The effect sizes were moderate, according to the clinical expert consulted on this review. In clinical practice, exercise capacity is usually assessed by exercise tests such as stair climbing or distance walked. The clinical relevance of the exercise outcome measures reported in the included systematic reviews are therefore uncertain. Results from two meta-analyses showed no significant difference in muscle strength between somatropin and placebo. Observational data from another review suggested that somatropin improved muscle strength during the first five years of treatment, but the effect was not sustained thereafter.

The effect of somatropin on lipid profile remains uncertain given conflicting results for TC, LDL, and HDL. One systematic review reported small reductions in total cholesterol and low-density lipoprotein with

the use of somatropin in patients older than 60 years: 4% to 8% reductions in TC and 11% to 16% reductions in LDL. According to the clinical expert, these reductions in cholesterol may be meaningful, since even small changes in cholesterol are associated with a reduced risk of cardiovascular events. The positive impact of somatropin therapy on BMD on different body sites was demonstrated in one meta-analysis; however, its long-term effect on BMD varied from trial to trial in another systematic review. Inconsistent results for body composition were observed in the four systematic reviews that reported this outcome, although statistically significant increases in lean body mass and decreased fat mass related to the use of somatropin were reported in two meta-analyses. The clinical expert indicated that even small increases in lean body mass and reductions in body fat could be beneficial and clinically meaningful, although no evidence was found in the literature to suggest minimally important differences for these outcomes. There was no compelling evidence available for the effect of somatropin on mortality, since data were scarce.

Most of the included systematic reviews and meta-analyses did not specify the type of somatropin products being evaluated, except the Hazem et al. review. The dose of Genotropin in this review ranged from 0.4 mg to 1.8 mg per day (assuming 80 kg of body weight). The recommended dosing for Genotropin in adults with GHD is 0.15 to 0.3 mg per day (maximum of 1.33 mg per day) in the product monograph. Therefore, the dose adopted in the clinical trials was higher than that approved by Health Canada, and this may impact the generalizability of the findings to Canadian clinical practice.
Evidence from the placebo-controlled RCTs of Genotropin, which were restricted to six months of treatment, suggested favourable effects on body composition, but other benefits such as improvements in HRQoL were inconsistently observed. Other purported benefits of Genotropin such as on lipid profile and BMD were also not consistently observed. The clinical significance of the body composition effects is uncertain for a number of reasons. First, the trials were small in terms of sample size and of short duration; hence, long-term effects in the general adult GHD population are uncertain. Second, it is unknown whether the observed changes predict clinical end points such as cardiovascular events or mortality. It is also noteworthy that the included trials did not enrol patients older than 60 years of age; therefore, evidence for Genotropin in the elderly is scant. The risks of adverse events during the six-month treatment were numerically higher in the Genotropin group compared with placebo.

All somatropin products have some similarities in manufacturing processes in that all products use recombinant DNA technology in *E. coli* host cells, except for Saizen. The excipients used as preservatives or stabilizers vary greatly between formulations (lyophilized powder and solution) as well as among products. Pharmacokinetic profiles of various somatropin products are slightly different from each other; however, these differences do not appear to be significant and are not expected to result in important clinical consequences. In addition, the clinical expert indicated that there was no apparent difference in efficacy and safety between different somatropin drugs in clinical practice, although differences in dosing and administration formats may add complexity when a patient is switched from one product to another.

5. CONCLUSIONS

There was no evidence to assess the relative efficacy and safety of Genotropin versus other somatropin products available in Canada for the treatment of adults with GHD. While all somatropin products have the same amino acid sequence as endogenous human GH and similar pharmacokinetic profiles, they differ somewhat with respect to manufacturing processes, dosage forms, excipients, dosing recommendations, and approved indications. Systematic reviews of somatropin products for the treatment of adult GHD indicate possible improvements in some dimensions of HRQoL, exercise performance, lipid profile, and body composition compared with placebo or no treatment, although results were inconsistent across studies for some outcomes, and the clinical importance of the observed changes is uncertain. The only consistent benefit of Genotropin in the manufacturer-submitted placebo-controlled RCTs was improved body composition, but, once again, the effects were of uncertain clinical significance.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patients Supplying Input

Due to the absence of an organized patient group for AGHD in Canada, input was received from individual patients. Two patients with AGHD provided input:

- Patient A — a woman diagnosed in 1982 as having AGHD as a result of severe head trauma, and
- Patient B — a woman who had been treated by transphenoidal resection and radiation for Cushing disease.

Both women live in British Columbia. Patient A has been in contact with Eli Lilly, the maker of Humatrope (somatropin), in an effort to coordinate with other AGHD patients and to encourage provincial funding of somatropin for AGHD. Patient B is one of the recipients of funding from Eli Lilly to start an advocacy group for AGHD patients.

2. Condition and Current Therapy-Related Information

Patient A had used human GH injections in the past, but had not used them for 17 years. In the meantime, she tried antidepressants and melatonin to control anxiety and depression, diet and exercise to maintain her weight, and an inhaler to control what was presumed to be asthma. None were effective. She suffered from hypoglycemia, which led to anxiety, depression, an inability to do strenuous physical activity, muscle cramps due to lactic acidosis, amenorrhea, and difficulty sleeping. The combination of hypoglycemia and insomnia left her "foggy," greatly reducing her ability to focus on tasks such as driving and affecting her productivity at work. In May 2012, her coworkers found her barely conscious at her desk, and she was taken to the hospital where her post-prandial blood sugar was 3.8 mmol/L and her insulin-like growth factor-1 (IGF-1) was in the mid-20s ng/mL rather than the 86 ng/mL to 271 ng/mL range appropriate for her gender and age. She experienced severe suicidal thoughts after this episode. A questionnaire administered by her endocrinologist indicated struggles with mood, social relations, and sleep loss.

Patient A's caregiver reported unpredictable and uncontrollable mood swings; he felt helpless to do anything but constantly monitor and attempt to calm her to ensure that no harm came to her or those around her.

Patient A noted that doctors were reluctant to prescribe GH as it is not recognized as being beneficial for those with AGHD. However, given her recurring depression, social isolation, and suicidal ideation, she believed the long-term risks of somatropin treatment were negligible compared with her current quality of life and was thus desperate to try it.

Patient B postponed trying GH therapy for four years due to financial constraints. She was required to work, as she is the primary breadwinner in her family, but was unable to do anything else due to fatigue. Instead of participating in her life or spending time with her husband and young son, she needed to sleep for up to 16 hours a day, and her sleep was interrupted up to 10 times a night. She also experienced osteopenia, leading to multiple fractures due to accidents that should have caused only minor injuries.

3. Related Information About the Drug Being Reviewed

Although neither patient has used Genotropin — Patient A has experience with Humatrope and Patient B with Omnitrope — both consider the benefits and barriers to access of somatropin in general to be relevant.

After slowly increasing her dose of somatropin, Patient A no longer suffers from hypoglycemia or lactic acidosis, and her IGF-1 is within the normal range. Her mental health has improved dramatically and, apart from an occasional burning sensation at the injection site, she has suffered no adverse effects after a year of use. The control of her hypoglycemia has allowed her to resume physical exercise, reducing her risk of diabetes and heart disease, and she now has better social relationships with friends, family, and colleagues. She finds the new pen devices considerably easier to use than the injections she used in the past, reducing the risk of over- or under-dosage. Patient A's employer reported that the lack of focus, lack of energy, and irritability that she displayed before starting on somatropin have tremendously improved, making her a much more positive and productive member of the team while greatly improving her personal well-being. Patient A has coverage for somatropin through her employer, but her lifetime benefits are limited, and she is concerned about what will happen when they run out.

Patient B credits somatropin with allowing her to become a functioning wife and mother for the first time in her child's life. After starting treatment, her sleep greatly improved, and she feels better both physically and cognitively. She is now able to take her son to swimming and Tai Kwon Do, she has taken up running again, feels stronger, and has the energy to meet with politicians, the media, and other patients to advocate for those with AGHD. She states she is terrified by the thought of having to do without treatment. She acknowledges that somatropin therapy is expensive, but sees the lack of coverage as a major barrier to the ability of patients with AGHD to be contributing members of society, regardless of their province of residence.

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
35	exp humans/
36	exp human experimentation/ or exp human experiment/
37	human.po.
38	or/35-37
39	34 not 38

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
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. Clinical study report: TRN 91-081-01. The effect of somatropin (Genotropin®) replacement therapy in GH-deficient adults on body composition, quality of life, bone mineral density, respiratory muscle strength, serum lipids, immune function, serum IGF-1 and safety [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Kabi Pharmacia AB; 1993 Jan 14.
2. Clinical study report: TRN 91-081-02. The effect of somatropin (Genotropin®) replacement therapy in GH-deficient adults on body composition, quality of life, bone mineral density, cardiovascular function, serum lipids, coagulation factors, serum IGF-1, insulin sensitivity and safety. A final report of randomized, double-blind, placebo-controlled study. [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Kabi Pharmacia AB; 1993 Oct 20.
3. Clinical study report: TRN 91-131-04. The effect of somatropin (Genotropin®) replacement therapy in GH-deficient adults on body composition, bone mineral content, bone mineral density, serum IGF-1, serum IGFBP-3 and safety. A final report of a randomized, double blind, placebo-controlled study [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Pharmacia AB; 1996 Aug 30.
4. Clinical study report TRN 91-131-08. The effect of somatropin (Genotropin®) replacement therapy in GH-deficient adults on body composition, quality of life, bone mineral density, serum IGF-1, exercise and safety. A final report of a randomized, double blind, placebo-controlled study (6 months) followed by open somatropin replacement (6 months) [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Pharmacia AB; 1996 Jan 31.
5. Clinical study report: CTN 92-8124-011. The effect of somatropin (Genotropin®) replacement therapy in GH-deficient adults on body composition, hand grip strength, quality of life, serum IGF-1, lipid metabolism and safety [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Pharmacia AB; 1996 Mar 12.
6. Clinical study report:TRN ***91-001***. The effect of somatropin (Genotropin) replacement therapy in growth hormone deficiency adults on body composition, quality of life, bone mineral density, muscle strength, exercise capacity, serum IGF-1, plasma lipids and safety. A report of a randomised, double-blind, 6-month placebo-controlled study and 24-month somatropin replacement therapy [**CONFIDENTIAL** internal manufacturer's report]. Stockholm: Pharmacia & Upjohn AB; 1997 Jun 18.
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