CDEC FINAL RECOMMENDATION

SOMATROPIN
(Genotropin – Pfizer Canada Inc.)
Indication: Growth Hormone Deficiency in Adults

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Genotropin be listed for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) with the following condition:

Condition
- List in a manner similar to other somatropin products for the treatment of adults with GHD.

Reasons for the Recommendation:
1. There is no evidence to suggest differential pharmacokinetic and pharmacodynamic properties of Genotropin compared with other somatropin products available in Canada.

2. At the submitted price, Genotropin ($[redacted] per day) is less costly than Humatrope ($49 per day), Nutropin ($82 per day), and Omnitrope ($41 per day).

Of Note:
CDEC noted that, as per the indication for replacement of endogenous growth hormone in adults, there are a limited number of adult patients for whom growth hormone therapy is appropriate.

Background:
Genotropin is a recombinant human growth hormone with an amino acid sequence that is identical to the growth hormone of the human pituitary gland. Genotropin is indicated for the following:
- Replacement of endogenous growth hormone in adults with GHD who meet either of the following two criteria:
  - Adult onset: patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma
  - Childhood onset: patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

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- Long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone.
- Treatment of growth failure in short children born small for gestational age and who fail to achieve catch-up growth by two to four years or later.
- Treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.
- Long-term treatment of idiopathic short stature.

This Common Drug Review (CDR) submission is for the treatment of GHD in adults. The recommended dose of Genotropin for the treatment of GHD in adults is 0.15 mg per day to 0.3 mg per day, administered subcutaneously. The final dose should be individually increased with respect to age and gender to a maximum maintenance dose of 1.33 mg per day. Genotropin is available as lyophilized powder for reconstitution in pre-filled pens: 5 mg, 5.3 mg, and 12 mg in Genotropin GoQuick; and 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 in Genotropin MiniQuick.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of Genotropin, two submissions by individual patients about their experiences with GHD and with somatropin products other than Genotropin, and a critique of the manufacturer's pharmacoeconomic evaluation. No RCTs met the inclusion criteria for the CDR systematic review. Specifically, no RCTs comparing Genotropin with other somatropin products for the treatment of adults with GHD were identified. Therefore, CDEC considered the following information:

- a summary of placebo-controlled RCTs of Genotropin in adults with GHD
- a summary of systematic reviews of somatropin treatment in adults with GHD
- pharmacokinetic data of somatropin products available in Canada.

Patient Input Information

The following is a summary of key information provided by two adults with GHD who, because there are not yet any adult GHD patient groups in Canada, responded to the CDR call for patient input:

- Both patients attribute a variety of serious physical (including low energy, insomnia, and weakness) and mental health problems (including depression) they have experienced to the condition.
- Both patients say their quality of life, including their ability to care for their children and, at least for one, her ability to work was greatly diminished by the condition.
- The individuals noted that their symptoms were significantly improved after receiving treatment with somatropin and expressed concern at the possibility of not having access to it in the future.

Placebo-controlled Trials

The manufacturer's submission included the following six placebo-controlled RCTs: CTN 92-8142-011 (N = 20), TRN 91-001 (N = 20), TRN 91-081-01 (N = 25), TRN 91-081-02 (N = 23), TRN 91-131-04 (N = 32), TRN 91-131-08 (N = 52). All trials included a six-month double-blind treatment period, during which patients received Genotropin or placebo, followed by an open-label treatment period where patients received Genotropin for up to 24 months. Genotropin was administered as a daily subcutaneous injection at a dose of 0.04 mg per kg per

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week for the first month of treatment and 0.08 mg per kg per week for subsequent months. Key efficacy and safety end points from the placebo-controlled trials are reported as follows:

- Statistically significant decreases in body fat were reported in all six RCTs favouring Genotropin compared with placebo (all $P < 0.05$).
- Statistically significant increases in lean body mass were reported in four RCTs favouring Genotropin compared with placebo (TRN 91-001, TRN 91-081-02, TRN 91-131-04, TRN 91-131-08; all $P < 0.05$). There was no statistically significant difference between Genotropin and placebo for lean body mass in two RCTs (TRN 91-081-01, CTN 92-8142-011).
- Statistically significant improvements in health-related quality of life, lipid profiles, and bone mineral density were not consistently observed across the RCTs.
- Adverse events were more frequently reported in the Genotropin groups compared with the placebo groups. Common adverse events observed in the Genotropin group included general disorders, peripheral swelling, and musculoskeletal disorders.
- Total adverse events were reported as follows:
  - 23 events with Genotropin and 32 events with placebo (CTN 92-8142-011)
  - 21 events with Genotropin and 1 event with placebo (TRN 91-001)
  - 36 events with Genotropin and 2 events with placebo (TRN 91-081-02)
  - 64 events with Genotropin and 44 events with placebo (TRN 91-131-04)
  - 125 events with Genotropin and 57 events with placebo (TRN 91-131-08)
  - 32 patients with Genotropin and 21 patients with placebo (TRN 91-081-01).
- Serious adverse events were reported as follows:
  - 0 events with Genotropin and 3 events with placebo (CTN 92-8142-011)
  - 1 event in both the Genotropin and placebo groups (TRN 91-001)
  - 2 events with Genotropin and 0 events with placebo (TRN 91-081-02)
  - 3 events with Genotropin and 1 event with placebo (TRN 91-131-04)
  - 2 events with Genotropin and 0 events with placebo (TRN 91-131-08)
  - 3 patients in the Genotropin group and 1 patient in the placebo (TRN 91-081-01)
- There were no withdrawals due to adverse events reported for any of the six RCTs.

Systematic Reviews

A systematic literature search by CDR identified eight systematic reviews comparing somatropin with placebo or no treatment in adults with GHD. The systematic reviews varied with respect to the inclusion of controlled and uncontrolled trials, patient characteristics, and outcome measures. Key efficacy and safety end points from the systematic reviews are as follows:

- Conflicting results were reported for changes in health-related quality of life, muscle strength, lipid profile, bone mineral density, and body composition.
- Statistically significant improvements in exercise capacity were reported for patients treated with somatropin compared with placebo-treated patients.
- Adverse events, serious adverse events, withdrawals due to adverse events, change in insulin-like growth factor-1 levels, and tumour occurrence were not reported in any of the systematic reviews.

Pharmacokinetics and Pharmacodynamics

CDR reviewed and summarized the pharmacokinetic and pharmacodynamic properties of the following somatropin products: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin. The information was obtained from the Canadian product monographs.

The pharmacokinetic properties of the different somatropin products appear to be similar.

The pharmacodynamic properties of Genotropin appear to be similar to Omnitrope; however,

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there is limited information on the pharmacodynamic properties of the other somatropin products available in Canada.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis, considering only drug acquisition costs, comparing Genotropin with the other somatropin products available in Canada for the treatment of GHD in adults (i.e., Humatrope, Saizen, Nutropin, and Omnitrope). The manufacturer assumed similar clinical effectiveness with Genotropin compared with other somatropin products for the treatment of adults with GHD. This assumption was based on the results of one RCT comparing Genotropin with Omnitrope for the treatment of GHD in children.

Based on CDR best estimates using maximum adult doses reported in the product monograph for each drug, Genotropin ($[redacted] per day) is less costly than Humatrope ($49 per day), Nutropin ($82 per day), and Omnitrope ($41 per day), but more costly than Saizen ($38 per day).

Other Discussion Points:

CDEC noted the following:

- The cost-effectiveness of somatropin therapy in adults with GHD requires evaluation.
- Multiple systematic reviews have not consistently shown clinical benefit of treatment with somatropin in adults with GHD. Where statistically significant findings have been reported (e.g., improvements in exercise capacity), there is a lack of clarity regarding the clinical importance of the results.
- The available evidence for use of somatropin in adults with GHD is limited by small patient numbers, short duration of follow-up, lack of evidence on clinically important outcomes, and limited generalizability to older patients.
- The current listing status of somatropin products for the treatment of GHD in adults varies across the CDR participating drug plans.
- The mode of administration varies across the different somatropin products, which may be an important factor for physicians and patients when selecting the appropriate treatment option.
- The patient input for this submission stated that their quality of life is negatively impacted by the condition; however, there were insufficient data in the submission to determine the effects of somatropin on the health-related quality of life of adults with GHD.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There were no RCTs comparing Genotropin with other somatropin products for the treatment of GHD in adults.
- There is no evidence demonstrating the comparative clinical benefit of somatropin treatment on clinically meaningful outcomes, such as mortality and fractures.

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CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

November 20, 2013 Meeting

Regrets:
One CDEC member could not attend the meeting.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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