CDEC FINAL RECOMMENDATION

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Genotropin be listed for the treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone with the following condition:

Condition
- List in a manner similar to other somatropin products for the treatment of children with growth hormone deficiency (GHD).

Reasons for the Recommendation:
1. One randomized controlled trial (RCT) demonstrated that the efficacy of Genotropin was similar to Omnitrope for improving height-related outcomes in children with GHD.

2. At the submitted price, Genotropin ($[redacted]) is less than Humatrope ($77 per day), Nutropin ($64 per day), Saizen ($59 per day), and Omnitrope ($42 per day).

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:
- 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.
- 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.

This Common Drug Review (CDR) submission is for the treatment of GHD in children. The recommended dose of Genotropin for children with GHD is 0.16 mg per kg per week to 0.24 mg per kg per week administered by subcutaneous injection. According to the product monograph, the dose of Genotropin should be adjusted based on the concentration of insulin-like growth factor-1 and adverse effects. 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 RCTs focused on Genotropin and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR call for patient input.

Clinical Trials
The CDR systematic review included two RCTs of children with GHD. The Romer study (reported in Romer et al. 2007 and 2009) was a nine-month, open-label, equivalence trial conducted in Europe. Eighty-nine patients were randomized (1:1) to either Genotropin (0.03 mg/kg/day) or Omnitrope (0.03 mg/kg/day). The doses in each group were readjusted to each patient's body weight after six months. The Shih study (reported in Shih et al. 1994) was a 12-month RCT conducted in Taiwan. Fifteen patients were randomized (1:1:1) to either Genotropin (0.1 IU/kg/day), Humatrope (0.1 IU/kg/day), or Saizen (0.2 IU/kg/three times per week). It was not specified if the doses could be adjusted during the Shih study, or if they were administered in a blinded or open-label manner.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- change from baseline in height
- change from baseline in height velocity
- change from baseline in height standard deviation score (HtSDS)
- change from baseline in height velocity standard deviation score (HVSDS)
- serious adverse events, total adverse events, and withdrawals due to adverse events.

All height-related outcomes were specified as primary outcomes in the Romer and Shih studies.

Results

Efficacy

- The efficacy results from the Romer study were reported as follows:
  - The mean difference in change in height velocity from baseline to study end between Genotropin and Omnitrope was –0.20 cm per year (95% CI: –1.34 to 0.94), which did not exceed the predefined equivalence margin of ± 2 cm per year.
  - The mean difference in change in height from baseline to study end between Genotropin and Omnitrope was 0.23 cm (95% CI: –0.59 to 1.06).

  - The mean difference in change in HtSDS from baseline to study end between Genotropin and Omnitrope was 0.12 (95% CI: –0.06 to 0.30).
  - The mean difference in change in HVSDS from baseline to study end between Genotropin and Omnitrope was 0.76 (95% CI: –0.57 to 2.10).
- In the Shih study, the mean changes in height from baseline to month 12 were 11.3 cm, 9.4 cm, and 11.1 cm in the Genotropin, Humatrope, and Saizen groups respectively. There were no statistical comparisons reported for any end points in the Shih study.

Harms (Safety and Tolerability)

- In the Romer study, the overall frequency of adverse events (based on all enrolled patients) was not reported; however, the frequency of individual adverse events (experienced by at least 5% of the enrolled population) including eosinophilia, elevated glycated hemoglobin, hematoma, and headache was comparable between the Genotropin and Omnitrope groups. The majority of adverse reactions were reported to be mild in intensity. There were no adverse events reported in the Shih study.
- There was one serious adverse event in the Romer study; however, it was unclear if the event occurred when the patient was being treated with Genotropin or Omnitrope. There were no serious adverse events reported in the Shih study.
- There were no withdrawals due to adverse events in either the Romer or Shih studies.

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 children (i.e., Humatrope, Saizen, Nutropin, and Omnitrope). The manufacturer assumed equivalent clinical efficacy of Genotropin with other somatropin drugs based on the results of the Romer study, which compared Genotropin with Omnitrope in children with GHD.

Based on CDR best estimates using the submitted price of $[redacted], the daily cost of the maximum dose of Genotropin ($[redacted]) is less than Humatrope ($77 per day), Nutropin ($64 per day), Saizen ($59 per day), and Omnitrope ($42 per day).

Other Discussion Points:

CDEC noted the following:

- The RCTs that met the inclusion criteria of the CDR review were limited by the small number of patients and short duration of follow-up.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Evidence from RCTs comparing Genotropin with other somatropin products available in Canada for the treatment of children with GHD.
- There is limited quality of life data about the treatment of children who have GHD with Genotropin.

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*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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