CDEC FINAL RECOMMENDATION

SOMATROPIN
(Genotropin – Pfizer Canada Inc.)
Indication: Turner Syndrome

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Genotropin be listed for the treatment of short stature associated with Turner syndrome (TS) in patients whose epiphyses are not closed, with the following condition:

Condition:
- List in a manner similar to other somatropin products for the treatment of TS.

Reasons for the Recommendation:
1. Somatropin is effective for the treatment of short stature associated with TS and there is no evidence to suggest that Genotropin has differential pharmacokinetic and pharmacodynamic properties compared with other somatropin products available in Canada.

2. At the submitted price, Genotropin ($[redacted]) is less costly than Humatrope ($100 per day), Nutropin ($84 per day), and Saizen ($96 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:
- Treatment of short stature associated with TS in patients whose epiphyses are not closed.
- 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.
- Long-term treatment of idiopathic short stature.
- Replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
  - Adult onset: patients who have growth hormone deficiency, 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 short stature associated with TS in patients whose epiphyses are not closed. The recommended dose of Genotropin in patients with TS is 0.33 mg/kg per week divided into six to seven doses and administered by subcutaneous injection. Dosage should be adjusted for the individual patient. 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 and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the call for patient input. There were also no RCTs that met the minimum inclusion criteria for the CDR systematic review; therefore, CDEC considered the following information:

- the results of two RCTs (Study 055 and Study 092) that were excluded from the CDR systematic review
- a summary of systematic reviews of somatropin treatment in patients with TS
- a summary of the properties of somatropin products available in Canada.

Study 055 and Study 092

CDEC considered the findings of two open-label RCTs, Study 055 and Study 092, that did not meet the inclusion criteria of the CDR systematic review. In both studies, patients with TS were treated with Genotropin alone or Genotropin plus hormonal therapy (ethinyl estradiol or oxandrolone in Studies 055 and 092 respectively). Twenty-two patients in Study 055 and 16 patients in Study 092 were treated with Genotropin alone for 12 months at doses ranging from 0.13 mg to 0.33 mg/kg per week. The standard deviation score (SDS) for height velocity and height were expressed using the Tanner (Study 055) or Sempé (Study 092) standards for age-matched children without TS as well as the Ranke standard (both studies) for age-matched, untreated TS patients. Change from baseline in the height-related end points for patients treated with Genotropin alone in Study 055 and Study 092 were reported as follows:

- Height velocity was 3.7 cm per year (95% CI: 3.0 to 4.3) in Study 055 and 2.2 cm per year (95% CI: 1.5 to 2.9) in Study 092.
- Height velocity SDS was 4.6 (95% CI: 3.5 to 5.6) in Study 055 (Tanner standard) and 2.2 (95% CI: 1.4 to 3.0) in Study 092 (Sempé standard).
- Height velocity SDS (Ranke Standard) was 4.3 (95% CI: 3.5 to 5.0) in Study 055 and 2.7 (95% CI: 1.8 to 3.5) in Study 092.
- Height SDS (Tanner standard) was 0.4 (95% CI: 0.3 to 0.6) in Study 055 and 0.3 (95% CI: 0.1 to 0.4) in Study in 092 (Sempé standard).
- Height SDS (Ranke Standard) was 0.8 (95% CI: 0.7 to 0.9) in Study 055 and 0.5 (95% CI: 0.4 to 0.5) in Study 092.

Systematic Reviews

A systematic literature search by CDR on the effects of somatropin in girls with TS identified two systematic reviews comparing somatropin with placebo or no treatment. The included studies in these reviews varied with respect to study design (RCTs or comparative observational studies), patient characteristics, and outcome measures. A meta-analysis was performed in one review. Data on final height, height velocity, health-related quality of life, and adverse events were assessed in both systematic reviews. The systematic reviews demonstrated that treatment with

somatropin resulted in more rapid growth and greater gains in height compared with no treatment. There was insufficient evidence to assess if treatment with somatropin improves the quality of life of patients with TS compared with no treatment.

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, 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 indicated for use in TS patients in Canada (i.e., Humatrope, Saizen, and Nutropin). The manufacturer assumed similar clinical effectiveness with Genotropin compared with other somatropin products. This assumption was based on the results of one trial comparing Genotropin with Omnitrope for the treatment of growth hormone deficiency in children, which suggested that there is similar efficacy between the two products. However, there are no data to support the assumption of similar efficacy in patients with TS, and there are no head-to-head trials against any other active comparator in patients with TS.

Based on CDR best estimates using the submitted price of $[redacted], the daily cost of the maximum dose of Genotropin ($[redacted]) is less than that of Humatrope ($100; 0.375 mg/kg per week), Nutropin ($84; 0.375 mg/kg per week), and Saizen ($96; 0.320 to 0.375 mg/kg per week).

Other Discussion Points:

CDEC noted the following:

- The listing status of somatropin for the treatment of TS varies across the CDR participating drug plans.
- There is uncertainty regarding the clinical importance of the increased growth observed with somatropin treatment in patients with TS. It would have been helpful to CDEC to have objective quality of life data or to have heard from patient groups regarding the difference the increased growth associated with somatropin would make to patients' quality of life.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There were no RCTs comparing Genotropin with other somatropin products available in Canada for the treatment of patients with TS.
- There are no substantive quality of life data for the treatment of TS 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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