CEDAC FINAL ADVICE – SUBSEQUENT ENTRY BIOLOGIC

SOMATROPIN
(Omnitrope – Sandoz Canada Inc.)
Indication: Growth Hormone Deficiency in Adults and Children

Advice:
The Canadian Expert Drug Advisory Committee's (CEDAC's) advice on Omnitrope is that drug plans consider a similar reimbursement policy for Omnitrope as for other growth hormone products.

When providing advice on Omnitrope the Committee considered the following:

Efficacy or Effectiveness

- One open-label randomized controlled trial demonstrated that in children Omnitrope had similar efficacy compared with Genotropin, which is the reference biologic drug used by Health Canada to assess Omnitrope and which is not marketed in Canada. Although there were limitations in the trial such as a short follow-up time, the Committee considered that the appropriate outcomes were evaluated to establish that the efficacy of Omnitrope was similar to Genotropin.
- There are no randomized controlled trials evaluating the clinical effectiveness of Omnitrope in adults. A systematic search by CDR on the effects of growth hormone and growth hormone deficiency in adults identified five meta analyses, three of which included clinical outcomes of interest. There were few statistically significant differences in the outcomes assessed for growth hormone compared with placebo, and statistically significant differences were of uncertain clinical importance. Therefore, there is little evidence of clinical benefit resulting from trials of recombinant growth hormone products in adults that might be extrapolated to Omnitrope.

Harms (Safety and Tolerability)

- Serious adverse events were similar between Omnitrope and Genotropin patients in the open-label randomized controlled trial. A greater proportion of Omnitrope patients developed antibodies compared with Genotropin patients. This issue appeared to be resolved through changes to the Omnitrope manufacturing process and location. Regardless, the clinical impact of antibody development is unknown. There is otherwise no signal that harm with Omnitrope would differ from Genotropin.

Pharmacokinetics

- Omnitrope has an identical peptide composition as endogenous human growth hormone. Health Canada considered that pharmacokinetic parameters measured in adults were similar between Omnitrope and Genotropin. There are no trials comparing the pharmacokinetics of Omnitrope to growth hormone products marketed in Canada, therefore, the Committee could not comment on the pharmacokinetic profile of Omnitrope relative to products marketed in Canada.

Comparator Human Growth Hormone Products

- There are three other recombinant human growth hormone products on the Canadian market with the same indication as Omnitrope. Reasons for a patient to choose an initial growth hormone product or to switch from one product to another may be related to practical patient considerations such as injection site reactions and the ability or willingness to reconstitute a powder form. Other issues considered by patients and physicians when selecting a treatment include dosage forms, drug concentrations, administration devices and the use of benzyl alcohol as a preservative in some products. There is no evidence of the effect of switching between Omnitrope and other Canadian growth hormone products on outcomes.

Cost and Cost-Effectiveness

- In the treatment of children, Omnitrope is less expensive than other somatropins, although the extent of the cost savings depends on a patient's weight.
- In adults, Omnitrope is less expensive than other somatropins at starting doses, but it is more expensive than Saizen and Nutropin at maximum doses.

Background:

Omnitrope is the first drug reviewed by Health Canada as a subsequent entry biologic (SEB) and evaluated by the Common Drug Review (CDR) in the Subsequent Entry Biologics Pilot Process. It is indicated for the treatment of growth hormone deficiency in children and adults. It is a recombinant human growth hormone with an amino acid sequence that is identical to the growth hormone of the human pituitary gland.

The Health Canada recommended dose in children is 0.025 mg/kg to 0.035 mg/kg once daily by subcutaneous injection. The recommended starting dose of Omnitrope in adults is 0.15 mg to 0.3 mg daily; in adults the final dose should be individualized to a maximum of 1.33 mg.

Although both powder and solution formulations of Omnitrope were approved by Health Canada, Omnitrope is only marketed in Canada as a solution. Pharmacokinetic and pharmacodynamic data have established similarity between the two Omnitrope formulations. Omnitrope is available in cartridges of 5 mg/1.5 mL or 10 mg/1.5 mL.

Other recombinant human growth hormone products available in Canada for the treatment of growth hormone deficiency are: Humatrope, Nutropin, and Saizen. Genotropin, which is the reference biologic used by Health Canada to assess Omnitrope, is not marketed in Canada.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of Omnitrope, comparator information on other recombinant growth hormone products available in Canada, and a critique of the manufacturer's pharmacoeconomic evaluation.

No RCTs met the inclusion criteria of the CDR systematic review as there were no trials identified that compared Omnitrope with placebo or with standard therapies marketed in Canada.

While no RCTs met the systematic review inclusion criteria, the CDR review summarized one RCT that compared Omnitrope with Genotropin. The open-label trial (N=89) was conducted in untreated prepubertal children with growth hormone deficiency. It evaluated two Omnitrope formulations (solution and powder) and Genotropin. At baseline patients were randomized to either Omnitrope powder or Genotropin powder. The trial design was complex with four different phases, including a switch from Genotropin to Omnitrope solution at nine months. There were also changes to the manufacturing process of Omnitrope products that occurred at nine months. There were no statistically significant differences in any of the growth parameters, including height and height velocity, between any of the different formulations of recombinant human growth hormone that were compared. At nine months, the mean difference (MD) for Omnitrope powder compared with Genotropin for height (cm) and height velocity (cm/year) were: MD = 0.23 (95% CI: -0.57 to 1.1) and MD -0.23 (95% CI: -1.37 to 0.91).

Serious adverse events were similar between Omnitrope and Genotropin patients in the trial. Common adverse events in both Omnitrope and Genotropin groups included hematoma, eosinophilia, and elevated glycated hemoglobin. Treatment-related hypothyroidism was more commonly observed with Omnitrope compared to Genotropin (14% versus 4% respectively). No patients had anti-growth hormone antibodies at baseline, however at nine months the proportion of patients with anti-growth hormone antibodies was 57% and 2% for Omnitrope and Genotropin groups, respectively. Between nine and 15 months, patients received Omnitrope products (powder and solution) manufactured in a different location using a modified process and a reduction in anti-growth hormone antibodies was observed. The clinical impact of antibody development is unknown.

No RCTs were identified that evaluated Omnitrope in adults. A systematic search by CDR on the effects of growth hormone and growth hormone deficiency in adults identified five meta analyses, of which three included outcomes of interest and were reviewed, none of which provided evidence of clinically important benefits of recombinant human growth hormone in adults.

Recombinant human growth hormone products indicated for the treatment of growth hormone deficiency vary with respect to formulations, excipient content, delivery devices, and dosing recommendations, which adds complexity if a patient requires a switch to another recombinant human growth hormone product. Patient preferences are a factor in deciding which growth hormone product to initiate and the decision is often made in conjunction with the child and family. Similarly, patient preferences influence switching from one product to another;

for example, patients experiencing burning at the injection site may want to switch to another growth hormone product. Treatment guidelines and health technology assessment reports relevant to the treatment of both children and adults with growth hormone deficiency did not provide guidance on switching or evidence on the effects of switching between growth hormone products. There are no studies comparing Omnitrope with other recombinant human growth hormone products marketed in Canada that would provide information on patient preferences, therefore, there is no trial information to guide decisions in switching from an existing product to Omnitrope.

The annual cost of Omnitrope is $5,687 to $7,961 in children (based on 20 kg weight) and $1,706 to $15,127 in adults (regardless of weight). In the treatment of children, Omnitrope is less expensive than other somatropins, although the extent of the cost savings depends on patient's weight. For a patient weighing 20 kg, Omnitrope costs approximately $15 to $22 daily versus $25 to $43 daily for comparators.

In adults, Omnitrope (approximately $5 to $9 daily) is less expensive than other growth hormone products (approximately $14 to $44) at starting doses, but more expensive than Saizen and Nutropin at maximum doses (approximately $44 compared with $28 to $35 daily).

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
Dr. Michael Allan, Dr. Lindsay Nicolle.

Conflicts of Interest:
CEDAC members reported no conflicts of interest related to this submission.

About this Document:
CEDAC provides formulary listing recommendations and advice to publicly funded drug plans.

This CEDAC Advice – Subsequent Entry Biologic (SEB) is provided in accordance with the SEB pilot project details outlined in CDR Update – Issue 62, which are in effect for the duration of the pilot project.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation or provided advice. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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