somatropin for injection, 5mg/mL vial of powder and solvent for solution for subcutaneous injection and 3.3mg/mL and 6.7mg/mL penfill cartridge of solution for subcutaneous injection (Omnitrope®) No. (598/10)

Sandoz Ltd

15 January 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

somatropin (Omnitrope®) is accepted for use within NHS Scotland for:

Infants, children and adolescents

- Growth disturbance due to insufficient secretion of growth hormone (GH)
- Growth disturbance associated with Turner syndrome
- Growth disturbance associated with chronic renal insufficiency
- Growth disturbance (current height standard deviation score (SDS) <–2.5 and parental adjusted SDS <–1) in short children/adolescents born small for gestational age, with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity SDS <0 during the last year) by four years of age or later
- Prader-Willi syndrome (PWS) disturbance due to insufficient secretion of growth hormone, for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults

- Replacement therapy in adults with pronounced GH deficiency. Patients with severe GH deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a GH deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic –pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those who have low insulin-like growth factor 1 (IGF-1) concentrations (SDS <-2), who may be considered for one test. The cut-off point of the dynamic test should be strict.

Somatropin (Omnitrope®) is a biosimilar product and has demonstrated equivalency in terms of efficacy and safety to a reference recombinant human growth hormone (somatropin (Genotropin®)).

The British National Formulary advises that it is good practice to use the brand name when prescribing biological medicinal products.

Overleaf is the detailed advice on this product.

Chairman, Scottish Medicines Consortium

Indication

Infants, children and adolescents

- Growth disturbance due to insufficient secretion of growth hormone (GH)
- Growth disturbance associated with Turner syndrome (TS)
- Growth disturbance associated with chronic renal insufficiency (CRI)
- Growth disturbance (current height standard deviation score (SDS) <–2.5 and parental adjusted SDS <–1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below –2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS <0 during the last year) by four years of age or later.
- Prader–Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults

- Replacement therapy in adults with pronounced GH deficiency. Patients with severe GH deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a GH deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those who have low insulin-like growth factor 1 (IGF-1) concentrations (SDS <-2), who may be considered for one test. The cut-off point of the dynamic test should be strict.

Dosing information

The recommended dose varies according to the condition being treated:

Children: 0.025–0.035 mg/kg/day for GH deficiency, 0.045–0.050 mg/kg/day for TS and CRI and 0.035 mg/kg/day for PWS and children/adolescents born SGA.

Adults: the initial dose is 0.15-0.3mg/day. Dosage should be adjusted according to serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved which rarely exceeds 1.0mg/day. GH requirements may decrease with age.

GH is self-administered at home as a subcutaneous injection. The injection site should be varied to prevent lipoatrophy.

After reconstituting the **powder for solution for injection** and the first use, the cartridge should remain in the pen for a maximum of 21 days.
After first use of the **solution for injection** the cartridge should remain in the pen for a maximum of 28 days.
The cartridges should be stored in the original pen in order to protect from light and be kept in a refrigerator (2℃ - 8℃).

Diagnosis and therapy with somatropin should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with growth disorders.

Product availability date

12 April 2006

Summary of evidence on comparative efficacy

In 2006, Omnitrope® was the first medicinal product to be licensed by the European Medicines Agency as a 'similar biological medicinal product' or 'biosimilar'. Omnitrope® is a recombinant human growth hormone (rhGH) which possesses 191 amino acids, the sequence of which is identical to that of natural hGH and is produced in a genetically modified strain of E. coli.

Two phase III multicentre pivotal studies were designed to demonstrate comparable efficacy and safety to the reference medicinal product somatropin (Genotropin®) in children with growth failure secondary to GH deficiency. For both studies, 24-month interim results are available. Patients were pre-pubertal with a height at least 2 SDs below the mean height for chronological age (CA) and sex and had a spontaneous height velocity (HV) at least 1 SD below the mean HV for CA and sex according to the standards of Tanner (British data: study 1) or Prader (Swiss data: study 2). Patients had documented child bone age (BA) radiography, a maximal hGH serum concentration of <10 nanograms/mL after two recommended GH stimulation tests and a full-term weight of over 2,500g. In addition, in study 2, patients were >2 years and had a BA ≤ 9 years in girls and ≤ 10 years in boys. In both studies patients received a subcutaneous (sc) dose of somatropin at bedtime; the total daily dose was calculated at baseline and adjusted to each patient's body weight at baseline and at each scheduled visit.

The first study was randomised, controlled and open-label, and consisted of three consecutive sub-studies in the same cohort of 89 previously untreated children. The objective of the first sub-study (part 1) was to demonstrate over 9 months that Omnitrope® powder for reconstitution was similar in terms of efficacy and safety to the reference product Genotropin®. The objective of part 2 was to demonstrate the similar efficacy and safety of Omnitrope® powder for reconstitution and Omnitrope® solution for injection over 6 months. The objective of the third part was to demonstrate the long term efficacy and safety of Omnitrope® solution for injection over 69 months, extending the total treatment period to 84 months. In part 1, patients received 0.03mg/kg Omnitrope® 5mg/mL powder for reconstitution (group A) or Genotropin® 5mg/mL (group B) in a 1:1 ratio. In part 2, patients who had received Omnitrope® powder continued to receive this, and patients who had received Genotropin® were switched to Omnitrope® 3.3mg/mL solution for injection. In part 3 all patients received Omnitrope® solution for injection. An equivalence margin for comparison between groups A and B was defined for the primary endpoint height velocity SD score (HVSDS) in the intention-to treat (ITT) population, corresponding to 1 SD (i.e. 2.8) or a HV of about 2cm/year. At baseline patients were aged approximately 7.6 years, with a mean BA of 4.9 years and a mean weight of 20kg. Group A had a higher proportion of males than group B and the baseline height was greater, though not significantly different (113cm versus 109cm; HSDS –2.95 versus –3.10). Baseline HV was 3.8cm/year versus 3.9cm/year in groups A and B respectively (HVSDS –2.3 in both groups).

In both studies, the primary efficacy endpoints evaluated the development of body height over time and included body height, height SD score (HSDS), HV and HVSDS. Secondary endpoints evaluated the time course of the hGH-induced serum parameters, insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP-3).

In part 1, the difference in mean HVSDS between Omnitrope® powder for solution for injection and the reference product after nine months was 0.86 (95% Confidence Interval (CI): -0.48 to 2.20). The baseline-adjusted difference was 0.76 (95% CI: -0.57 to 2.10); the 95% CI was within the specified equivalence margin of 2.8.

Other baseline-adjusted differences were -0.20 cm/yr (95% CI: -1.34 to 0.94) for mean HV, 0.23cm (95% CI –0.59 to 1.06) for mean height and 0.12 (95% CI –0.06 to 0.30) for HSDS. Similar effects were found for the secondary endpoints.

In part 2, the difference in mean HVSDS between Omnitrope® powder for reconstitution and Omnitrope® solution for injection at 15 months was –0.81 (95% CI: –1.91 to 0.29). The baseline adjusted difference in HV was -0.14 cm/yr (95% CI: -0.98 to 0.70) and in HVSDS was 0.75 (95% CI: -0.37 to 1.86). Similar effects were also found for height and HSDS and for the secondary endpoints.

Mean HV peaked at three months, decreased slightly between three and six months, and continued to decrease slightly but steadily thereafter. Mean height continued to increase throughout the study. Thus, for example, the mean height at 24 months was 132cm in group A and 127cm in group B, representing HSDS of –1.70 and –1.94 respectively and a baseline-adjusted difference for height of 0.15cm (0.17 for HSDS).

The long term efficacy and safety results from part 3 were to be reported separately.

The second study was non-comparative, non-controlled and open-label. The objectives were to demonstrate the efficacy and safety of Omnitrope® powder for reconstitution in the treatment of 51 previously untreated children and to confirm its low immunogenic potential. All patients received 0.03mg/kg Omnitrope® 5mg/mL powder for reconstitution. At baseline patients were aged approximately 8.0 years, with a mean BA of 6.2 years and a mean weight of 20kg. Mean baseline height was 112cm (HSDS –2.97) and mean HV was 3.72cm/year (HVSDS –2.52). For each of the primary and secondary study endpoints, the mean differences between baseline and all later visits were statistically significant. As in study 1, HV peaked and then declined. Mean height at 24 months increased by 17cm to 129cm (HSDS –1.76), and 64% (n=32/50) of patients had reached a body height that was within the range of normally growing children of the same CA and sex.

Summary of evidence on comparative safety

In study 1 Omnitrope® was found to have a similar safety profile to that of the reference product Genotropin®, with the exception of antibody formation (see below), and to be comparable with the known adverse reaction profile of rhGH. Events were generally mild in intensity. In part 1, adverse events (AEs) experienced by at least 5% of patients who received Omnitrope® powder for reconstitution were hypothyroidism (11%), eosinophilia (11%), increased glycated haemoglobin levels (9%), and headache (7%). AEs associated with Genotropin® use included injection-site haematoma (9%), eosinophilia (7%), increased glycated haemoglobin levels (7%) and headache (7%). In part 2, patients who received Omnitrope® powder predominantly experienced eosinophilia (5%) and headache (5%). AEs associated with Omnitrope® solution for injection were eosinophilia (8%), injection site haematoma (7%) and increased glycated haemoglobin levels (5%).

One patient experienced a serious adverse reaction; worsening of scoliosis which required several hospitalisations.

Antibody formation with high concentrations of host cell proteins that enhance anti-growth hormone (GH) antibodies occurred in group A early in the comparative study: 24/41 patients had developed anti-GH antibodies within 9 months compared with one patient in group B. The product administered to group A during part 1 of this study was non-commercial, and the products administered later in the study had been further purified. All patients in Group B received Genotropin in part 1, and were then switched to Omnitrope in parts 2 and 3.

Thereafter, the number of patients with anti-GH antibodies declined in group A, remained ≤2 in group B and was zero in the non-comparative study. No unexpected developments were observed in part 3, although the results will be reported separately.

Summary of clinical effectiveness issues

The biosimilar products Omnitrope® powder for reconstitution and Omnitrope® solution for injection have demonstrated comparable quality, efficacy and safety to the reference product Genotropin® in children with growth failure secondary to GH deficiency, one of its licensed indications. Omnitrope® has been granted a licence for the same wide range indications as for Genotropin® on the basis of this indicator of equivalence.

The reference product (Genotropin®) has only been directly compared to an early non-commercial product of Omnitrope® powder used in part 1 of study 1 and over nine months. However given the sustained growth in later parts of the study, when patients were transferred to the commercial powder product (and then the solution), it was concluded that the commercial product of Omnitrope® powder used in part 2 of study 1 and in study 2 was similar in terms of efficacy to the early product: the additional purification steps introduced to reduce immunogenicity did not affect the efficacy of the commercial product.

Omnitrope® was well tolerated and demonstrated similar comparability to the reference product not only in equivalent therapeutic efficacy but also in terms of safety and immunogenicity. Further long term safety data are being collected.

Omnitrope® as solution for injection is easier for the patient to use than a powder as no reconstitution step is required, though it is not the only somatropin product to offer this advantage. SMC experts note that, as rhGH products have comparable therapeutic efficacy, product choice depends on patients' ease of use of the injection device.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing somatropin (Omnitrope®) with two other somatropin products (Genotropin® and Norditropin®). Equivalence between Omnitrope® and Genotropin® (the reference product) was established based on two phase III clinical trials of children with growth failure secondary to GH deficiency and was assumed to generalise to the other indications covered by the licence. Resource use associated with treatment initiation and monitoring costs were taken from the NICE HTA of GH deficiency and assumed to apply equally across all arms. Drug costs were estimated according to the dose required for each indication and based on the mean patient weight in the clinical trials. Based on drug costs, the manufacturer estimated that treatment with Omnitrope® in paediatric patients resulted in savings of between £1,089 and £1,724 per year versus Genotropin® and between £692 and £1,096 per year versus Norditropin®, depending on the indication. In adult patients a saving of £537 was estimated versus Genotropin® and £341 versus Norditropin®.

Some weaknesses of the analysis were noted:

- No clinical data were presented to support the assumption of equivalent efficacy between Omnitrope® and Norditropin®. The manufacturer based this assumption on the NICE HTA of GH deficiency which did not distinguish between treatments in terms of efficacy.
-

- No clinical evidence was presented to support the use of Omnitrope® in other indications. The clinical studies were conducted in children with GH deficiency and it has been assumed that the evidence from these trials would generalise to the other indications covered by the licence.

Based on drug costs alone, Omnitrope® is associated with savings compared with Genotropin® and Norditropin®.

The assumption of equivalent efficacy between treatments was accepted together with a view that efficacy results based on studies in GH deficiency can be generalised to the other indications, therefore the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The following National Institute for Health and Clinical Excellence (NICE) guidance in children has been approved by the Health Technology Board for Scotland and the NICE guidance in adults has been approved by NHS Quality Improvement Scotland through its revised procedure of processing NICE Guidance. These NICE guidelines predate the licensing of Omnitrope® for growth hormone deficiency.

NICE; Technology Appraisal (TA) 42. Guidance on the use of human growth hormone (somatropin) in children with growth failure: guidance published May 2002.

NICE; TA 64. Human growth hormone (somatropin) in adults with growth hormone deficiency: guidance published August 2003

NICE indicate that a multiple technology appraisal entitled 'Growth failure (in children) – human growth hormone (hGH) (review) is in progress. The expected date of issue is May 2010.

Additional information: comparators

Other biosynthetic human growth hormone (somatropin) comparators include Genotropin®, Humatrope®, Norditropin®, Saizen®, Zomacton®, and NutropinAq®.

Cost of relevant comparators

The recommended dose varies according to the condition being treated. For the purpose of a cost comparison, the indication of GH deficiency in children has been calculated.

Drug	Dose regimen	Cost per year (£)
Omnitrope®	**0.025 to 0.035 mg/kg/day by subcutaneous (sc) injection**	**3,324 to 4,654**
Genotropin®	0.025 to 0.035 mg/kg/day by sc injection	4,219 to 5,907
Saizen®	0.025 to 0.035 mg/kg/day by sc injection	4,006 to 5,609
Norditropin®	0.025 to 0.035 mg/kg/day by sc injection	3,893 to 5,450
NutropinAq®	0.025 to 0.035 mg/kg/day by sc injection	3,767 to 5,274
Zomacton®	0.025 to 0.035 mg/kg/day by sc injection	3,626 to 5,076
Humatrope®	0.025 to 0.035 mg/kg/day by sc injection	3,276 to 4,586

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30 October 2009. Costs were calculated for an 8 year-old child weighing 20kg which were baseline characteristics in the pivotal studies and the dose for GH deficiency is recommended by NICE TA 42.

Additional information: budget impact

The manufacturer estimated savings of £103k in year 1 and £89k in year 5. It was assumed that Omnitrope® would replace 10% of the Genotropin® market with the market share assumed to remain constant over the 5 year period, equating to use of Omnitrope® in 143 patients per year.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Biosimilar medicines. A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (the 'biological reference medicine'). The active substance of a biosimilar medicine similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.

This assessment is based on data submitted by the applicant company up to and including ***09 November 2009.***

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Romer T, Peter F, Saenger P et al. Efficacy and safety of a new ready-to-use recombinant human growth hormone solution. J Endocrinol Invest 2007; 30: 578–589.

European Medicines Agency (EMEA). European public assessment report (EPAR) for somatropin (Omnitrope®). EMEA/H/C/607. Published 23/04/08. http://www.emea.europa.eu/humandocs/Humans/EPAR/omnitrope/omnitrope.htm

Tanner JM, Whitehouse RH, Takaishi, M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965, Part II. Arc Dis Child 1966,41: 61 3-35.

Prader A, Largo RH, Molinari L, lssler C. Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl 1989,52: 1-1 25.