AUSTRALIAN PRODUCT INFORMATION

HUMATROPE® (SOMATROPIN, RBE) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

HUMATROPE® (somatropin).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HUMATROPE is a highly purified preparation and is available in cartridges containing 6 mg (18 IU*), 12 mg (36 IU*), or 24 mg (72 IU*) somatropin and when reconstituted with the diluent provided the cartridge contains 2.07 mg/mL, 4.17 mg/mL or 8.46 mg/mL somatropin respectively. Each cartridge also contains the inactive ingredients: mannitol, glycine and dibasic sodium phosphate heptahydrate and is supplied with an accompanying diluent. The diluent contains water for injections, metacresol and glycerol (see section **6.5 Nature and contents of container** and section **6.4 Special precautions for storage**). The glycerol in the diluent ensures the tonicity of the reconstituted product is within acceptable ranges. Reconstituted solutions have a pH of approximately 7.5.

3. PHARMACEUTICAL FORM

HUMATROPE is a sterile, white, lyophilised powder intended for subcutaneous or intramuscular administration after reconstitution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

HUMATROPE is indicated for the long-term treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone.

HUMATROPE is also indicated for the treatment of growth disturbances associated with gonadal dysgenesis (Turner syndrome).

HUMATROPE is also indicated for the treatment of adults with severe growth hormone deficiency 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 growth deficiency.

* The specific activity of the International Standard for somatropin is defined as 3 International Units per mg of protein. HUMATROPE is now labelled based on a specific activity of 3 IU/mg and was formerly labelled based on a specific activity of 2.7 IU/mg.

In patients with childhood onset isolated GH deficiency) no evidence of hypothalamic-pituitary disease or cranal irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations ≤2 SDS who may be considered for one test. The cut-off point of the dynamic test should be strict.

HUMATROPE is also indicated for the treatment of growth retardation in prepubertal children with chronic renal insufficiency whose height is on or less than the twenty-fifth percentile and whose growth velocity is on or less than the twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 30 mL/min/1.73 m2.

HUMATROPE is also indicated for the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years (see section **5.1 Pharmacodynamic properties - Clinical trials**).

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage and administration schedule for HUMATROPE should be individualised for each patient.

Dosage

Children with endogenous growth hormone deficiency

The dosage and administration schedule for HUMATROPE should be individualised for each patient. Generally, the recommended weekly dosage is 0.177-0.255 mg/kg (0.53-0.765 IU/kg) of body weight. The maximal replacement weekly dosage is 0.26 mg/kg (0.78 IU/kg) of bodyweight. It should be divided into equal doses given on 3 alternate days, 6 times per week or daily. The subcutaneous route of administration is preferable; intramuscular injection is also acceptable.

Girls with Turner Syndrome

The recommended weekly or daily dosage is show in Table 1. The weekly dosage should be divided into 6 to 7 subcutaneous injections to be administered, preferably in the evening.

Table 1. Weekly and Daily Dosage Information by Body Weight

Weekly Dosing	
mg/kg/week	0.17 to 0.375
IU/kg/week	0.5 to 1.125
mg/M^2/week	5 to 11
IU/M^2/week	15 to 34
Daily Dosing	
Mg/kg/day	0.024 to 0.054

The optimal concurrent sex steroid therapy has not been determined. In clinical studies (see section **5.1 Pharmacodynamic properties - Clinical trials**), ethinyloestradiol was commenced at age 13 at 2.5 μg per day, was increased to 5.0 μg per day at age > 14 and increased to 20 μg per day plus medroxyprogesterone acetate 10 mg cyclically at age 15.

Small for Gestational Age

The recommended dosage is 0.033 to 0.067 mg/kg body weight per day given as a subcutaneous injection. Very short children (i.e., height SDS <–3) and/or older pubertal children: it is recommended to start treatment with larger doses of somatropin (eg 0.067 mg/kg/day), and to reduce the dosage gradually towards 0.033 mg/kg/day if substantial catch-up growth is observed during the first few years of therapy. Younger SGA children (eg, approximately <4 years) with less severe short stature (baseline height SDS values between -2 and -3): it is recommended to start treatment at a lower dose (eg, 0.033 mg/kg/day) and titrate the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the somatropin dose as necessary.

Adult Patients

Either a non-weight based or a weight-based dosing regimen may be followed, with doses adjusted based on treatment response, side effects and serum insulin-like growth factor I (IGF-I) concentrations. Dose requirements may decline with increasing age and may differ between male and female patients.

The dosage of somatropin should be decreased in cases of persistent oedema or severe paraesthesia, in order to avoid the development of carpal tunnel syndrome.

Non-weight based dosing: A starting dose of approximately 0.2 mg/day (range, 0.15 – 0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1 – 2 months by increments of approximately 0.1 - 0.2 mg/day.

Weight-based dosing: The recommended starting dosage is not more than 0.006 mg/kg (6 µg/kg) daily. The dosage may be increased according to individual patient requirements to a maximum of 0.0125 mg/kg (12.5 µg/kg) daily.

Elderly patients

Elderly patients may be more sensitive to the action of HUMATROPE and therefore may be more prone to develop adverse effects. A lower starting dose and smaller dose increments should be considered for older patients.

Prepubertal children with growth retardation secondary to Chronic Renal Insufficiency

The recommended dose is 0.045 mg/kg – 0.050 mg/kg (approximately 0.14 IU/kg) of body weight per day, given as a daily subcutaneous injection.

Obese patients

Obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen.

Administration

Each HUMATROPE cartridge should be reconstituted using the accompanying diluent syringe. **See Reconstitution Instruction Leaflet for comprehensive directions on HUMATROPE cartridge reconstitution**.

The resulting solution should be clear, without particulate matter. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

The cartridges have been designed for use only with the HUMATROPE injection device. The diluent syringe is for single use only. Discard it after use. A sterile needle should be used for each administration of HUMATROPE.

4.3 CONTRAINDICATIONS

HUMATROPE should not be used when there is any evidence of activity of a tumour. Intracranial lesions must be inactive and anti-tumour therapy completed prior to the institution of somatropin therapy. HUMATROPE should be discontinued if there is evidence of tumour growth.

HUMATROPE cartridges should not be used if the patient is allergic to metacresol or glycerol.

HUMATROPE should not be used for growth promotion in children with closed epiphyses.

HUMATROPE should not be initiated to treat patients with acute critical illness due to complications following open heart surgery or abdominal surgery, multiple accident trauma, or to patients having acute respiratory failure (see section **4.4 Special warnings and precautions for use**).

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The effects of somatropin on recovery were studied in two placebo-controlled clinical trials involving 522 adult patients who were critically ill due to complications following open heart or abdominal surgery, multiple accidental trauma, or who were having acute respiratory failure. Mortality was higher (41.9% vs. 19.3%) among somatropin treated patients (doses 5.3 – 8 mg/day) compared to those receiving placebo. The safety of continuing somatropin in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation in patients having acute critical illnesses should be weighed against the potential risk.

Cartridges should be reconstituted only with the supplied diluent. Cartridges should not be reconstituted with any other solution.

If injected subcutaneously, the injection sites should be rotated to minimise the risk of lipoatrophy.

Myositis is a very rare adverse event that may be related to the preservative metacresol. In the case of myalgia or disproportionate pain at the injection site, myositis should be considered. Cartridges should not be used if the patient is allergic to metacresol or glycerin.

Therapy with HUMATROPE should be directed by physicians who are experienced in the diagnosis and management of paediatric patients with growth disorders or adult patients with growth hormone deficiency.

Experience with prolonged treatment in adults is lacking.

Treatment in growth hormone deficient adults should be attempted only after definitive treatment of pituitary tumour (if present) is completed and all other pituitary hormone deficiencies are corrected as clinically indicated.

Patients who were treated with somatropin for growth hormone deficiency during childhood until attainment of final (adult) height should be re-evaluated for growth hormone deficiency

after epiphyseal closure and before replacement therapy is commenced at the doses recommended for adults.

Paediatric Use

For paediatric patients, treatment should be continued until the end of the growth has been reached. It is advisable not to exceed the recommended dosage in view of the potential risks of acromegaly, hyperglycaemia and glucosuria.

Girls with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear or hearing disorders.

Intracranial Lesion

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Abnormal Glucose Metabolism and Diabetes Mellitus

Because somatropin may induce a state of insulin resistance, patients who receive somatropin should be observed for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin. Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents.

Glucocorticoid replacement therapy

If glucocorticoid replacement therapy is required, glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects. In patients treated with somatropin, previously undiagnosed secondary hypoadrenalism may be unmasked, and such patients may require glucocorticoid replacement therapy.

Hypopituitarism/ Hypothyroidism

In patients with hypopituitarism (multiple pituitary hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered. Hypothyroidism may develop during treatment with human growth hormone and inadequate treatment of hypothyroidism may prevent optimal response to human growth hormone. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Intracranial Hypertension

In cases of severe or recurrent headache, visual problems, nausea and/or vomiting, fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, somatropin treatment should be discontinued. At present, there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

Slipped Capital Epiphysis

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses. Any child with the onset of a limp during growth hormone therapy should be evaluated.

Children born SGA

In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In children born SGA it is recommended to measure fasting plasma insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (eg familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs growth hormone should not be administered until the patient has been stabilised for diabetes care. Then growth hormone may be introduced with careful monitoring of the diabetic metabolic control. An increase in insulin dosage may be required.

In children born SGA it is recommended to measure the plasma IGF-I concentration level before the start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels exceed +2 SD compared to references for sex, age and pubertal status, the IGF-I / IGFBP-3 ratio should be taken into account to consider dose adjustment.

Initiating HUMATROPE treatment in children born SGA near onset of puberty is not recommended because of limited experience.

Chronic Renal Insufficiency

Before instituting treatment with HUMATROPE for growth retardation secondary to chronic renal insufficiency, patients should have been followed for one year to verify growth disturbance. Conservative treatment for renal insufficiency should have been established and should be maintained during treatment. Treatment with HUMATROPE should be discontinued at the time of renal transplantation.

Prader-Willi Syndrome

There have been reports of sleep apnoea and sudden death in paediatric patients with Prader-Willi syndrome receiving somatropin treatment who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection. In patients with growth hormone deficiency, who also have Prader-Willi syndrome, physicians should consider the benefit-risk ratio when prescribing somatropin. HUMATROPE is not indicated in patients who have Prader-Willi syndrome.

Secondary neoplasms in survivors of childhood cancer

In childhood cancer survivors, an increased risk of a second neoplasm (benign and malignant) has been reported in patients treated with somatropin. Intracranial tumors, in particular meningiomas in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. However, in childhood cancer survivors, no increased risk of primary cancer recurrence has been reported with somatropin treatment.

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated these patients should be carefully monitored for development of neoplasms.

Monitor patients receiving somatropin therapy carefully for increased growth, or potential malignant changes, of pre-existing nevi.

Pancreatitis in children

Children treated with somatropin may have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.

Progression of Scoliosis in Pediatric Patients

Progression or initial identification of scoliosis is often apparent in children during periods of rapid growth. As somatropin increases growth rate, patients with scoliosis who are treated with somatropin should be monitored for progression.

Use in the Elderly

Elderly patients may be more sensitive to the action of HUMATROPE and therefore may be more prone to develop adverse effects.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Gender differences have been demonstrated in responsiveness to GH by GH-deficient adults, with women requiring higher doses than men to achieve similar IGF-I responses, an effect that is accentuated by oral estrogen replacement in women. Orally administered estrogen suppresses GH dependent IGF-I production in the liver. In a study, women taking oral estrogen required higher doses of GH to achieve acceptable IGF-I concentrations than did age-matched men or women using transdermal estrogen. It has also been demonstrated that GH requirements are significantly higher for GH-deficient women receiving estrogen replacement (primarily by the oral route) than for eugonadal GH-deficient women.

Estrogen-replete women, whether pre-menopausal or post-menopausal, may need higher doses than men. Oral estrogen administration may increase the dose requirements of HUMATROPE in women.

Somatropin can increase cytochrome P450 (CYP) enzyme activity in humans and may result in reduced plasma concentrations and decreased effectiveness of drugs metabolised by CYP3A such as sex steroids, cyclosporine and some anticonvulsants.

Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents.

If glucocorticoid replacement therapy is required, glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects. In patients treated with somatropin, previously undiagnosed secondary

hypoadrenalism may be unmasked, and such patients may require glucocorticoid replacement therapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies in animals have not been conducted to assess the effect of HUMATROPE on fertility.

Use in pregnancy

Category B2.

Animal reproduction studies have not been conducted with HUMATROPE. It is not known whether HUMATROPE can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Somatropin should be given to a pregnant woman only if clearly needed.

Use in lactation

There have been no studies conducted with HUMATROPE in nursing mothers. It is not known whether HUMATROPE is excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when somatropin is administered.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS

Adverse effects identified from clinical trials

Paediatric Patients

In clinical trials in growth hormone deficient patients, approximately 2% of the patients developed antibodies to growth hormone. Nevertheless, even these patients had expected increases in linear growth and other beneficial effects of human growth hormone and did not have any unusual side effects. Although growth-limiting antibodies have been observed with other growth hormone preparations (including products of pituitary origin), antibodies in patients treated with HUMATROPE have not limited growth. The long-term implications of antibody development are uncertain at this time.

In addition to an evaluation of compliance with the treatment program and of thyroid status, testing for antibodies to human growth hormone should be carried out in any patient who fails to respond to therapy.

Common (≥1% and <10%)

A mild and transient oedema, which appeared in 2.5% of patients, was observed early during the course of treatment. Progression of scoliosis, injection site pain and hypersensitivity to the diluent (metacresol/glycerine) have also been reported.

Uncommon (≥0.1% and <1%)

Lipoatrophy has been reported following subcutaneous injection of human growth hormone. Cases of hyperglycaemia have also been reported.

Rare (≥0.01% and <0.1%).

Some rare cases of benign intracranial hypertension and localised muscle pain have been reported.

Very Rare (<0.01%)

Gynaecomastia and insomnia has been reported very rarely in paediatric patients.

Girls with Turner Syndrome

Very common (≥10%)

Hypothyroidism occurred in 13.5% of patients with Turner syndrome receiving HUMATROPE. This was not statistically significantly different from patients who received no treatment.

Common (≥1% and <10%)

Peripheral oedema occurred in 6.8% of patients with Turner syndrome receiving HUMATROPE. This was not statistically significantly different from patients who received no treatment.

Adult Patients

Very common (≥10%)

In the first 6 months of controlled blinded trials, adult onset growth hormone deficient adults experienced a statistically significant increase in oedema (HUMATROPE 17.3% vs placebo 4.4%, p=0.043) and peripheral oedema (11.5% vs 0% respectively, p=0.017).

In patients with adult onset growth hormone deficiency, oedema, muscle pain, joint pain and joint disorder were reported early in therapy and tended to be transient or responsive to dosage titration.

Common (≥1% and <10%)

Localised muscle pain, paraesthesias, gynaecomastia, insomnia, carpal tunnel syndrome and hyperglycaemia have been reported.

Uncommon (≥0.1% and <1%)

In clinical studies in which high doses of HUMATROPE were administered to healthy adult volunteers, the following events have occurred infrequently: headache, weakness, and glucosuria.

Adverse effects identified from spontaneous post marketing surveillance

Paediatric Patients

Uncommon (≥0.1% and <1%)

Type 2 diabetes mellitus has been reported.

Leukaemia has been reported in a small number of children who have been treated with growth hormone of pituitary origin, somatrem and HUMATROPE. The relationship, if any, between leukaemia and growth hormone therapy is uncertain.

Adult Patients

Common (≥1% and <10%)

Respiratory System: Dyspnoea, sleep apnoea

Vascular System: Hypertension

Adult cases of type 2 diabetes mellitus have been reported spontaneously.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Linear Growth - HUMATROPE stimulates linear growth in children who lack adequate normal endogenous growth hormone, in children with short stature in association with Turner syndrome and in prepubertal children with growth retardation secondary to chronic renal insufficiency.

In vitro, preclinical, and clinical testing have demonstrated that HUMATROPE is therapeutically equivalent to human growth hormone of pituitary origin and achieves equivalent pharmacokinetic profiles in normal adults. The bioavailability of HUMATROPE is slightly greater when given by the subcutaneous route than by the I.M. route. Treatment of growth hormone-deficient children and children with Turner syndrome with HUMATROPE produces increased growth rate and IGF-1 (Insulin-like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with human growth hormone of pituitary origin.

In addition, the following actions have been demonstrated for HUMATROPE and/or human growth hormone of pituitary origin.

A. Tissue Growth - 1. Skeletal Growth: HUMATROPE stimulates skeletal growth in patients with growth hormone deficiency, in patients with Turner syndrome and in prepubertal children with growth retardation secondary to chronic renal insufficiency. The measurable increase in body length after administration of either HUMATROPE or human growth hormone of pituitary origin results from an effect on the growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth-hormone-deficient children but increase during treatment with HUMATROPE. Elevations in mean serum alkaline phosphatase concentrations are also seen. 2. Cell Growth: It has been shown that

there are fewer skeletal muscle cells in short-statured children who lack endogenous growth hormone as compared with normal children. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

B. Protein Metabolism - Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with human growth hormone of pituitary origin. Treatment with HUMATROPE results in a similar decrease in serum urea nitrogen.

C. Carbohydrate Metabolism - Children with hypopituitarism sometimes experience fasting hypoglycaemia that is improved by treatment with HUMATROPE. Large doses of human growth hormone may impair glucose tolerance.

D. Lipid Metabolism - In growth hormone-deficient patients, administration of human growth hormone of pituitary origin has resulted in lipid mobilisation, reduction in body fat stores, and increased plasma fatty acids.

E. Mineral Metabolism - Retention of sodium, potassium, and phosphorus is induced by human growth hormone of pituitary origin. Serum concentrations of inorganic phosphate increased in patients with growth hormone deficiency after therapy with HUMATROPE or human growth hormone of pituitary origin. Serum calcium is not significantly altered in patients treated with either human growth hormone of pituitary origin or HUMATROPE.

Clinical trials

Turner Syndrome

In a randomised study to evaluate the efficacy of growth hormone for the treatment of patients with short stature due to Turner syndrome, 75 growth hormone treated patients were compared to a concurrent control group of 65 patients who received no growth hormone. The study was of open, randomised, parallel group design and compared HUMATROPE to no treatment (a placebo was not used). Ethinyloestradiol was commenced at age 13 and medroxyprogesterone acetate added at age 15. Patients were followed up to final height, achievement of which was defined by bone age >14 years and growth velocity <2 cm/year. A total of 27 patients in the HUMATROPE treated group and 19 patients in the untreated group were analysed as having completed the protocol. The HUMATROPE treated group, who received a dose of 0.3 mg/kg/week (given 6 times per week) from a mean age of 11.7 years for a mean duration of 4.7 years, attained a mean near final height of 146.0 ± 6.2 cm (n=27, mean ±SD) as compared to the control group who attained a near final height of 142.1 ± 4.8 cm (n=19). By analysis of covariance[1], the effect of growth hormone therapy was a mean height increase of 5.4 cm (p= 0.001). The study did not define the optimal dose, optimal age to commence therapy or optimise co-therapy with other hormonal therapy.

Adult Replacement Therapy

Two multicentre trials in adult onset growth hormone deficiency (n=98) and two studies in childhood onset growth hormone deficiency (n=67) were designed to assess the effects of

[1] Analysis of covariance includes adjustments for baseline height relative to age and for mid-parental height.

replacement therapy with HUMATROPE. The primary efficacy measures were body composition (lean body mass and fat mass), lipid parameters, and the Nottingham Health Profile. The Nottingham Health Profile is a general health-related quality of life questionnaire. These four studies each included a 6-month randomised, blinded, placebo controlled phase followed by 12 months of open label therapy for all patients. The HUMATROPE dosages for all studies were identical: one month of therapy at 0.00625 mg/kg/day followed by the proposed maintenance dose of 0.0125 mg/kg/day.

Adult onset patients and childhood onset patients differed by diagnosis (organic versus idiopathic pituitary disease), body size (normal versus small for mean height and weight), and age (mean = 44 versus 29 years). Lean body mass was determined by bioelectrical impedance analysis (BIA), validated with potassium 40. Body fat was assessed by BIA and sum of skinfold thickness. Lipid subfractions were analysed by standard assay methods in a central laboratory.

HUMATROPE treated adult onset patients, as compared to placebo, experienced an increase in lean body mass (2.59 versus –0.22 kg, $p<0.001$) and a decrease in body fat (-3.27 versus 0.56 kg, $p<0.001$). Similar changes were seen in childhood growth hormone deficient patients. These significant changes in lean body mass persisted throughout the 18 month period as compared to baseline for both groups, but for fat mass only in the childhood onset group. A decrease in the waist/hip ratio was seen in the adult, but not the child onset group. Some increase in body fat mass was seen in both studies during the second six months of treatment. Total cholesterol decreased short term (first 3 months) although the changes did not persist. However, the low HDL cholesterol levels observed at baseline (mean 0.78 mmol/L and 0.88 mmol/L in adult onset and childhood onset patients) normalised by the end of 18 months of therapy (a change of 0.35 and 0.29 mmol/L for the adult onset and childhood onset groups, $p<0.001$). Adult onset patients reported significant improvements as compared to placebo in the following 2 of 6 possible health related domains: physical mobility and social isolation. Patients with childhood onset disease failed to demonstrate improvements in Nottingham Health Profile outcomes. Placebo treated patients also improved against baseline scores. No long term morbidity or mortality data are available.

Prepubertal children with growth retardation secondary to chronic renal insufficiency

A total of 28 prepubertal children (5 female, 23 male) with growth retardation secondary to chronic renal insufficiency were enrolled in an open label, uncontrolled study to assess the efficacy and safety of treatment with HUMATROPE 0.057 mg/kg (0.17 IU/kg) per day. Twenty-five children received HUMATROPE for one year, 16 for two years and six for five years. Mean treatment duration was 2.9 years. The mean chronological age at baseline was 9.1 ± 3.2 years (range: 2.3 to 14.3 years). Efficacy was primarily assessed from changes from baseline in height standard deviation scores (SDS) and height velocity. Height was increased throughout HUMATROPE therapy with a progressive increase in height SDS at each yearly timepoint assessed. Sixteen children completed two years of therapy and gained a mean of 1.12 ± 0.60 height SD units. Six children completed five years of therapy and gained a mean of 1.83 ± 0.80 height SD units. Overall, for patients included in the efficacy analyses, the mean increase in height SDS at the last measurement of HUMATROPE therapy was 1.16 ± 0.77 from baseline (95%CI: 0.84 to 1.47, $p<0.001$). Height velocity increased at 2 years by a mean of 6.59 ± 2.82 SD units and at 5 years, by a mean of 6.42 ± 2.64 SD units. Overall, for patients included in the efficacy analyses, the mean increase in height velocity SDS at the last measurement of HUMATROPE therapy was 5.02 ± 3.17 from baseline (95%CI: 3.72 to 6.33, $p<0.001$). All of these changes were highly statistically significant. There are no studies of the use of HUMATROPE following renal transplantation.

Paediatric Patients Born Small for Gestational Age (SGA) Who Fail to Demonstrate Catch up Growth by Age 2 - 4 Years

Data from 2 clinical trials demonstrate the effectiveness of HUMATROPE in promoting linear growth in short children born SGA who fail to demonstrate catch-up growth.

The primary objective of Study 1 was to demonstrate that the increase from baseline in height SDS after 1 year of treatment would be similar when HUMATROPE is administered according to an individually adjusted dose (IAD) regimen or a fixed high dose (FHD) regimen. The height increases would be considered similar if the lower bound of the 95% confidence interval (CI) for the mean difference between the groups (IAD – FHD) was greater than -0.5 height SDS. This 2-year, open-label, multicenter, European study enrolled 193 prepubertal, non-GH deficient children with mean chronological age 6.8 ± 2.4 years (range: 3.0 to 12.3). Additional study entry criteria included birth weight <10th percentile and/or birth length SDS <-2 for gestational age, and height SDS for chronological age ≤-3. Exclusion criteria included syndromal conditions (eg, Turner syndrome), chronic disease (eg, diabetes mellitus), and tumor activity. Children were randomised to either a FHD (0.067 mg/kg/day [0.47 mg/kg/week]; n=99) or an IAD treatment group (n=94). The initial HUMATROPE dosage in the IAD treatment group was 0.035 mg/kg/day (0.25 mg/kg/week). The dosage was increased to 0.067 mg/kg/day in those patients in the IAD group whose 1-year height gain predicted at Month 3 was <0.75 height SDS (n=40) or whose actual height gain measured at Year 1 was <0.75 height SDS (n=11). Approximately 85% of the randomised patients completed 2 years of therapy.

At baseline, the FHD and IAD treatment groups had comparable height SDS (mean -3.9; Table 2). Although the mean 1-year height increase in the IAD group was statistically significantly lower than that observed in the FHD group, the study achieved its primary objective by demonstrating that the increase from baseline in height SDS in the IAD group was clinically similar (non-inferior) to that in the FHD group (mean between-group difference = -0.3 SDS [95% CI: -0.4, -0.2 SDS]). The mean changes from baseline in height SDS at the end of the 2-year study were 1.4 and 1.6 SDS in the IAD and FHD groups, respectively. The results were similar when children who entered puberty during the study were removed from the analysis.

Table 2. Study 1 – Results for Height SDS and Change from Baseline in Height SDS at Year 1 and Year 2 After HUMATROPE Treatment of Short Children Born SGA Who Fail to Demonstrate Catch-up Growth[a]

	IAD Group 0.035 to 0.067 mg/kg/day Mean (SD)	**FHD Group 0.067 mg/kg/day Mean (SD)**	**Between-Group Difference IAD – FHD[b]**
Baseline	(n=86) -3.9 (0.6)	(n=93) -3.9 (0.7)	-0.0 ± 0.1 (-0.2, 0.2) p-value = 0.95
Year 1 Height SDS Change from baseline	(n=86)[c] -3.0 (0.7) 0.9 (0.4)	(n=93)[c] -2.7 (0.7) 1.1 (0.4)	-0.3 ± 0.1 (-0.4, -0.2) p-value <0.001
Year 2 Height SDS Change from baseline	(n=82)[c] -2.5 (0.8) 1.4 (0.5)	(n=88)[c] -2.2 (0.7) 1.6 (0.5)	-0.3 ± 0.1 (-0.4, -0.1) p-value = 0.003

[a] Abbreviations: IAD=individually adjusted dose; FHD=fixed high dose; SD=standard deviation; SDS=standard deviation score

[b] Least squares mean difference ± standard error and 95% confidence interval based on ANCOVA model with treatment and gender as fixed effects, and baseline height SDS, baseline chronological age, baseline bone age, and mid-parental target height SDS as covariates.

[c] *Only children with actual height measurements were included in the Year 1 and Year 2 analyses*

Study 2 was an open-label, multicenter, single arm study conducted in France, during which 35 prepubertal, non-GH deficient children were treated for 2 years with HUMATROPE 0.067 mg/kg/day (0.47 mg/kg/week). Mean chronological age at baseline was 9.3 ± 0.9 years (range: 6.7 to 10.8). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age <-2. Exclusion criteria included syndromal conditions (eg, Turner syndrome), chronic disease (eg, diabetes mellitus), and any active disease. All 35 patients completed the study. Mean height SDS increased from a baseline value of -2.7 (SD 0.5) to -1.5 (SD 0.6) after 2 years of HUMATROPE treatment.

These studies were not designed as dose finding studies, nor were they designed to capture quality of life measures.

Some of the height gain obtained with treating short children born SGA with growth hormone may be lost if treatment is stopped before reaching final height.

5.2 PHARMACOKINETIC PROPERTIES

A dose of 100 micrograms(0.27 IU**)/kg to adult male volunteers will give a peak serum level (Cmax) of about 55 ng/mL, a half-life (t½) of nearly four hours and maximal absorption (AUC[0 to ∞]) of about 475 ng.hr/mL.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Somatropin showed no evidence of mutagenic activity in bacterial or mammalian cells and showed no activity in an assay for DNA damage in rodent hepatic cells.

Carcinogenicity

Associations between elevated serum IGF-1 concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

For full list of excipients, see section **2 Qualitative and Quantitative Composition**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before Reconstitution

Each HUMATROPE cartridge is stable for 3 years when refrigerated between (2°-8°C). The diluent syringes are stable for 3 years when stored below 30°C. Avoid freezing Diluent for HUMATROPE.

After Reconstitution

Each HUMATROPE Cartridge is stable for up to 28 days when reconstituted with diluent for HUMATROPE and refrigerated between 2° to 8°C. Avoid freezing reconstituted HUMATROPE. Daily room temperature exposure should not exceed 30 minutes after reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

Each HUMATROPE cartridge contains 6 mg (18 IU), 12 mg (36 IU) or 24 mg (72 IU) of human growth hormone and when reconstituted with the diluent provided the cartridge contains 2.07 mg/mL, 4.17 mg/mL or 8.46 mg/mL somatropin respectively The cartridge also contains the inactive ingredients mannitol, glycine and dibasic sodium phosphate. Phosphoric acid and/or sodium hydroxide may have been added at the time of manufacture to adjust the pH. The 6 mg cartridge is supplied in a combination package with an accompanying 3.17 mL syringe of diluting solution, and the 12 mg and 24 mg with an accompanying 3.15 mL syringe of diluting solution. The diluent contains water for injections with metacresol (0.3% for 6 mg, 12 mg and 24 mg diluent) as a preservative and glycerol (1.7% for 6 mg and 0.29% for 12 mg and 24 mg diluent).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

HUMATROPE (somatropin, rbe, for injection) is a polypeptide hormone of recombinant DNA origin. HUMATROPE has 191 amino acid residues and a molecular weight of about 22,125 daltons. The amino acid sequence of the peptide is identical to that of human growth hormone of pituitary origin. HUMATROPE is synthesised in a strain of Escherichia coli that has been modified by the addition of the gene for human growth hormone.

The biological effects of HUMATROPE are equivalent to human growth hormone of pituitary origin.

CAS number

CAS No.: 12629-01-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8. SPONSOR

Eli Lilly Australia Pty. Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

9. DATE OF FIRST APPROVAL

24 October 1995

10. DATE OF REVISION

20 November 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor address update

Adult indication included by direction of the Administrative Appeals Tribunal.