SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Humatrope 6 mg, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Humatrope 6 mg: The cartridge contains 6 mg of somatropin.
When reconstituted contains 2.08 mg/ml Humatrope 12 mg: The cartridge contains 12 mg of somatropin
When reconstituted contains 4.17 mg/ml Humatrope 24 mg: The cartridge contains 24 mg of somatropin
When reconstituted contains 8.33 mg/ml

Somatropin is produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is a white or almost white powder.

The solvent is a clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric Patients

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

Humatrope is also indicated for the treatment of short stature in children with Turner Syndrome, confirmed by chromosome analysis.

Humatrope is also indicated for the treatment of patients who have growth failure associated with SHOX deficiency, as confirmed by DNA analysis.

Humatrope is also indicated for the treatment of growth retardation in prepubertal children with chronic renal insufficiency.

Humatrope is also indicated for growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < - 1) in short children born small for gestational age (SGA), with a birth weight and/or length below – 2 SD, who failed to show catch up growth (height velocity SDS < 0 during the last year) by 4 years of age or later.

Adult Patients

Humatrope is indicated for replacement therapy in adults with pronounced growth hormone deficiency.

Patients with severe growth hormone 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 growth 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 having low IGF-I concentrations (<2SDS) who may be considered for one test. The cut-off point of the dynamic test should be strict.

4.2 Posology and method of administration

Posology

The dosage and administration schedule should be personalised for each individual; however for:

Growth hormone deficient paediatric patients

The recommended dosage is 0.025-0.035 mg/kg of body weight per day by subcutaneous injection. This is the equivalent to approximately 0.7-1.0 mg/m^2 body surface area per day.

Growth hormone deficient adult patients

The recommended starting dose is 0.15 – 0.30 mg/day. A lower starting dose may be necessary in older and obese patients.

This dose should be gradually increased according to individual patient requirements based on the clinical response and serum IGF-I concentrations.

Total daily dose usually does not exceed 1 mg.

IGF-I concentrations should be maintained below the upper limit of the age-specific normal range. The minimum effective dose should be used and dose requirements may decline with increasing age.

Women may require higher doses than men, with men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen therapy are under-treated while men are over-treated.

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 (see section 4.8).

Patients with Turner Syndrome
The recommended dosage is 0.045-0.050 mg/kg of body weight per day given as a subcutaneous injection to be administered preferably in the evening.

This is equivalent to approximately 1.4 mg/m^2 per day.

Prepubertal paediatric patients with Chronic Renal

Insufficiency
The recommended dosage is 0.045-0.050 mg/kg of body weight per day given as a subcutaneous injection.

Paediatric patients with SHOX deficiency
The recommended dosage is 0.045-0.050 mg/kg of body weight per day given as subcutaneous injection.

Paediatric patients born Small for Gestational Age (SGA)
The recommended dose is 0.035 mg/kg of body weight per day (equivalent to 1 mg/m^2 body surface area per day) given as a subcutaneous injection, until final height is reached (see section 5.1).

Treatment should be discontinued after the first year of treatment, if the height velocity SDS is below
+1.0 SDS. Treatment should be discontinued if height velocity is <2cm/year and, if confirmation is required, bone age is >14 years (girls) or >16 years (boys), corresponding to closure of epiphyseal growth plates.

Method of administration

Humatrope is administered by subcutaneous injection after reconstitution

The subcutaneous injection sites should be varied in order to avoid lipoatrophy.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.

Humatrope should not be reconstituted with the supplied solvent for patients with a known sensitivity to either metacresol or glycerol.

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

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure (see section 4.4).

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

The maximum recommended daily dose should not be exceeded (see section 4.2).

Previous paediatric subjects, who had been treated with growth hormone during childhood until final height was attained, should be re-evaluated for growth hormone deficiency after epiphyseal closure, before replacement therapy is commenced at the doses recommended for adults.

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

There is so far no evidence to suspect that growth hormone replacement influences the recurrence rate or regrowth of intracranial neoplasms, but standard clinical practice requires regular pituitary imaging in patients with a history of pituitary pathology. A baseline scan is recommended in these patients before instituting growth hormone replacement therapy.

In childhood cancer survivors, a higher risk of a second neoplasm (benign or malignant) has been reported in patients treated with somatropin. Intracranial tumours, in particular, were the most common of these second neoplasms.

In cases of severe or recurrent headache, visual problems, nausea and/or vomiting, a

fundoscopy for papilloedema is recommended. If papilloedema is confirmed a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone 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.

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

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may as such unmask incipient hypothyroidism. Monitoring of thyroid function should therefore be conducted in all patients.

In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

For paediatric patients, the 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.

Before instituting treatment with somatropin 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 (which includes control of acidosis, hyperparathyroidism and nutritional status for one year prior to the treatment) should have been established and should be maintained during treatment. Treatment with somatropin should be discontinued at the time of renal transplantation.

The effects of growth hormone 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 growth hormone treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. The safety of continuing growth hormone 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 risks.

If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see section 4.5). If a change of the route of oestrogen administration (oral to transdermal or vice-versa) is made, growth hormone should be newly titrated. An increasing sensitivity to growth hormone (expressed as change in serum IGF-I per growth hormone dose) over time may be observed, particularly in men.

Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or

stress doses, following initiation of somatropin treatment (see section 4.5).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Humatrope is not indicated for the treatment of patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

There have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy.

Elderly patients (age ≥65 years) are more sensitive to the action of Humatrope, they may be more prone to develop (severe) adverse events.

Experience in patients above 80 years is limited. Experience with prolonged treatment in adults is lacking.

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 (e.g. 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 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 and in children with SHOX deficiency near onset of puberty is not recommended because of limited experience.

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.

Pancreatitis

Although rare, pancreatitis should be considered in somatropin-treated patients who develop abdominal pain, especially in children.

Progression of scoliosis in paediatric patients

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium per dose (23mg), i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).

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, corticosteroids, cyclosporine and anticonvulsants.

4.6 Fertility, Pregnancy and lactation

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 reproduction capacity. Humatrope should be given to a pregnant woman only if clearly needed.

There have been no studies conducted with Humatrope in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humatrope is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Humatrope has no known effect on ability to drive or use machines.

4.8 Undesirable effects

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Immune system disorders

Hypersensitivity to solvent (metacresol/glycerol): 1 %-10 %
Hypersensitivity to the active substance: Frequency not known (cannot be estimated from the available data)

Endocrine disorders

Hypothyroidism: 1 %-10 %

Reproductive system and breast disorders

Gynaecomastia: 0.1 %-1 % paediatrics; 0.1 %-1 % adults

Metabolism and nutrition disorders

Mild hyperglycaemia: 1 % paediatrics; 1 %-10 % adults
Type 2 diabetes mellitus: 0.1 % - 1 % paediatrics; adult cases were reported spontaneously with unknown frequency
Insulin resistance

Nervous system disorders

Benign intracranial hypertension: 0.01 %-0.1 %
Headache: >10 % adults
Insomnia: <0.01 % paediatrics; 1 %-10 % adults
Paraesthesia: 0.01 %-0.1 % paediatrics; 1 % - 10 % adults
Carpal tunnel syndrome: 1 % - 10 % adults

Vascular disorders

Hypertension: <0.01 % paediatrics; 1 %-10 % adults

Respiratory, thoracic and mediastinal disorders

Dyspnoea: 1 %-10 % adults
Sleep apnoea: 1 %-10 % adults

Musculoskeletal and connective tissue disorders

Localised muscle pain (myalgia): 1 %-10 % adults; 0.01 % - 0.1 % paediatrics
Joint pain and disorder (arthralgia): >10 % adults

Progression of scoliosis: 1 %-10 % paediatrics

General disorders and administration site conditions

Weakness: 0.1 % -1 %
Injection site pain (reaction): 1 %-10 %
Oedema (local and generalised): 1 %-10 % paediatrics; 10 % adults

Investigations

Glucosuria: <0.01 % paediatrics; 0.01-0.1 % adults

Paediatric patients

In clinical trials with growth hormone deficient patients approximately 2 % of the patients developed antibodies to growth hormone. In trials in Turner Syndrome where higher doses were used, up to 8 % of patients developed antibodies to growth hormone. The binding capacity of these antibodies was low and growth rate was not affected adversely. Testing for antibodies to growth hormone should be carried out in any patient who fails to respond to therapy.

A mild and transient oedema was observed early during the course of treatment.

Leukaemia has been reported in a small number of children who have been treated with growth hormone. However there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposing factors.

Adult patients

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

Adult patients treated with growth hormone, following diagnosis of growth hormone deficiency in childhood, reported side effects less frequently than those with adult onset growth hormone deficiency.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdosage could result in signs and symptoms of acromegaly consistent with the known effects of excess human growth hormone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anterior pituitary lobe hormones and analogues, ATC code: H01A C01

Somatropin is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin. It 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. The most prominent effect of Humatrope is that it stimulates the growth plates of long bones.

Additionally, it promotes cellular protein synthesis and nitrogen retention.

Humatrope stimulates lipid metabolism: it increases plasma fatty acids and HDL-cholesterols and decreases total plasma cholesterol.

Humatrope therapy has a beneficial effect on body composition in growth hormone deficient patients, in that body fat stores are reduced and lean body mass is increased. Long term therapy in growth hormone deficient patients increases bone mineral density.

Humatrope may induce insulin resistance. Large doses of human growth hormone may impair glucose tolerance.

The data available from clinical trials so far in patients with Turner Syndrome indicate that, while some patients may not respond to this therapy, an increase over predicted height has been observed, the average being 3.3 ± 3.9 cm.

In a clinical trial, patients born SGA (mean age 9.5 ± 0.9 yr) who were treated with a Humatrope dose of 0.067 mg/kg/day for two years showed a mean gain in height SDS of +1.2 during treatment. The results obtained in this trial with Humatrope are comparable with those described for other recombinant growth hormone preparations.

<u>Paediatric Population</u>

An open-label, multicentre, observational study GeNeSIS (Genetics and Neuroendocrinology of Short Stature International Study) was established as a post-authorisation safety surveillance programme. Paediatric data on the final height standard deviation score gain in the approved indications are:

Growth hormone deficiency, 1.39 ± 1.14; Turner syndrome, 0.95 ± 0.82; short stature homeobox containing gene deficiency (SHOX-D), 0.86 ± 0.91; small for gestational age (SGA), 1.11 ± 0.96 and chronic renal insufficiency (CRI), 0.88 ± 0.81 after 6.0 ± 3.7, 6.4 ± 3.3, 4.7 ± 2.6, 5.4 ± 3.0, and 5.8 ± 2.8 years of somatropin treatment, respectively.

Results from the long-term observational study (GeNeSIS) of paediatric somatropin treatment included data from 22,311 somatropin-treated patients (63.0% growth hormone deficiency, 12.7% idiopathic short stature, 8.4% Turner syndrome, 5.7% children born small for gestational age, 2.6% SHOX deficiency, 0.4% chronic renal insufficiency, 5.5% other, and 1.7% unknown) and were consistent with the known safety profile of somatropin. Key safety objectives of incidence of type 2 diabetes, de novo cancers and mortality were assessed by comparison to contemporary general population registry data. Eighteen of the 21,448 somatropin-treated patients eligible for analysis developed type 2 diabetes mellitus in the study; however, 13 out of the 18 patients had reported pre-existing diabetes risk factors. The standardised incidence ratio (95% CI for type 2 diabetes in somatropin-treated children was significantly elevated [3.77 (2.24 to 5.96)], but the incidence at 16.8 cases per 100,000 person-years of exposure is rare. The standardised incidence ratio (95% CI) for all-sites primary cancers in patients with no previous cancer history was 0.71 (0.39 to 1.20), based on 14 cases. There were 45 reported deaths in somatropin-treated patients.

The standardised mortality ratio (95% CI), based on 42 deaths in patients who had follow-up during study, was 0.6 (0.4 to 0.8) for all-cause mortality for all short stature diagnoses combined; only the diagnostic subgroups of patients with a history of organic growth hormone deficiency, and in particular due to previous malignancy, had a significantly elevated standardised mortality ratio.

5.2 Pharmacokinetic properties

A dose of 100 µg/kg to adult male volunteers will give a peak serum level (C_{max}) of about 55 ng/mL, a half life ($t_{½}$) of nearly four hours and maximal absorption ($AUC_{[0\ to\ \infty]}$) of about 475 ng*hr/ml.

5.3 Preclinical safety data

Humatrope is human growth hormone produced by recombinant technology. No serious events have been reported in subchronic toxicology studies. Long term animal studies for carcinogenicity and impairment of fertility with this human growth

hormone (Humatrope) have not been performed. There has been no evidence to date of Humatrope induced mutagenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cartridges of powder: mannitol, glycine, dibasic sodium phosphate; phosphoric acid and sodium hydroxide.

Solvent syringes: glycerol, metacresol, water for injections, hydrochloric acid and sodium hydroxide.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before reconstitution: 3 years.

After reconstitution: The product may be stored for a maximum of 28 days at 2°C - 8°C.

Daily room temperature exposure should not exceed 30 minutes.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

Humatrope is available in the following pack sizes:

Humatrope 6 mg: 1 cartridge (glass type I) with 6 mg of powder for solution for injection, and 3.17 ml of solvent solution in a pre-filled syringe (glass type I) with a plunger (rubber). Pack size of 1, 5 and 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for preparation and handling:

Reconstitution: Each cartridge of Humatrope should be reconstituted using the accompanying solvent syringe. To reconstitute, attach the cartridge to the pre-filled solvent syringe and then inject the entire contents of the pre-filled solvent syringe into the cartridge. The solvent needle aims the stream of liquid against the glass wall of the cartridge. Following reconstitution, gently invert the cartridge up and down 10 times until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear, without particulate matter. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

Humatrope cartridges can be used in conjunction with compatible CE marked pen injection systems. The manufacturer's instructions with each individual pen must be followed for loading the cartridge, attaching the needle and administering the Humatrope injection.

The solvent syringe is for single use only. Discard it after use. A sterile needle should be used for each administration of Humatrope.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 14895/0290

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