ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Omnitrope 1.3 mg/ml powder and solvent for solution for injection

2. QUALITATIVE AND QUAN TITATIVE COMPOSITION

After reconstitution, one vial contains 1.3 mg somatropin* (correspond ing to 4 IU) per ml.
* produced in Escherichia coli by recombinant DNA technology. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white.
The solvent is clear and colourless

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (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 4 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 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 hormone 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 (SDS < -2) who may be considered for one test. The cut-off point of the dynamic test should be strict.

4.2 Posology and method of admin istration

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.

Posology
Paediatric population
The posology and administration schedule should be individualised.

Growth disturbance due to insufficient secretion of growth hormone in paediatric patients
Generally a dose of 0.025 - 0.035 mg/kg body weight per day or 0.7 - 1.0 mg/m^2 body surface area per day is recommended. Even higher doses have been used.

Prader-Willi syndrome, for improvement of growth and body composition in paediatric patients
Generally a dose of 0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day is recommended. Daily doses of 2.7 mg should not be exceeded. Treatment should not be used in paediatric patients with a growth velocity less than 1 cm per year and near closure of epiphyses.

Growth disturbance due to Turner syndrome
A dose of 0.045 - 0.050 mg/kg body weight per day or 1.4 mg/m^2 body surface area per day is recommended.

Growth disturbance in chronic renal insufficiency
A dose of 1.4 mg/m^2 body surface area per day (0.045 - 0.050 mg/kg body weight per day) is recommended. Higher doses may be needed if growth velocity is too low. A dose correction may be needed after six months of treatment (see section 4.4).

Growth disturbance in short children/adolescents born small for gestational age (SGA)
A dose of 0.035 mg/kg body weight per day (1 mg/m^2 body surface area per day) is usually recommended 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.

Treatment should be discontinued if height velocity is < 2 cm/year and, if con firmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to epiphyseal closure.

Dose recommendations for paediatric patients

Indication	mg/kg body weight dose per day	mg/m² body surface area dose per day
Growth hormone def iciency	0.025-0.035	0.7-1.0
Prader - Willi syndrome	0.035	1.0
Turner syndrome	0.045-0.050	1.4
Chronic renal insufficiency	0.045-0.050	1.4
Children/adolescents born small for gestational age (SGA)	0.035	1.0

Growth hormone deficient adult patients

Therapy should start with a low dose, 0.15 - 0.3 mg per day. The dose should be gradually increased according to individual patient requirements as determined by the IGF-I concentration. Treatment goal should be insulin -like growth factor (IGF-I) concen trations within 2 SDS from the age corrected mean of healthy adults. Patients with normal IGF-I concentrations at the start of the treatment should be administered growth hormone up to an IGF-I level into the upper range of normal, not exceeding the 2 SDS. Clinical response and side effects may also be used as guidance for dose titration. The daily maintenance dose rarely exceeds 1.0 mg per day. Women may require higher doses than men, while men show an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are under - treated while men are over - treated. The accuracy of the growth hormone dose should therefore be controlled every 6 months. As normal physiological growth hormone product ion decreases with age, dose requirements may be reduced. The minimum effective dose should be used.

Special populations
Elderly
Experience in patients above 60 years is limited.
Renal impairment
In chronic renal insufficiency, renal function should be below 50 percent of normal before institution of therapy. To verify growth disturbance, growth should be followed for a year preceding institution of therapy. During this period, conservative treatment for renal insufficiency (which includes control of acidos is, hyperparathyroidism and nutritional status) should have been established and should be maintained during treatment.

The treatment should be discontinued at renal transplantation.

To date, no data on final height in patients with chronic renal insuffici ency treated with Omnitrope are available.

Method of administration

The injection should be given subcutaneously and the site varied to prevent lipoatrophy.

For instructions for use and handling see section 6.6.

4.3 Contraindications

- Hypersensitivity to so matropin or to any of the excipients.
- Somatropin must not be used when there is any evidence of activity of a tumour.

Intracranial tumours must be inactive and anti tumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.

- Somatropin must not be used for growth promotion in patients with closed epiphyses.
- Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar

conditions must not be treated with somatropin. With regard to patients undergoing substitution therapy, see section 4.4.

4.4 Special warnings and precautions for use

Insulin sensitivity

Somatropin may induce a state of insulin resistance and in some patients hyperglycaemia. Therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria for diabetes mellitus type II may be fulfilled as a result of the somatropin therapy, but risk factors such as obesity (including obese PWS patients), family history, steroid treatment, or pre-existing impaired glucose tolerance have been present in most cases where this occurred. In patients with already manifested diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increasing hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of Omnitrope therapy. In growth hormone deficiency, secondary to treatment of malignant disease, it is recommended to pay attention to signs of relapse of the malignancy.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. Patients limping during treatment with somatropin, should be examined clinically.

Benign intracranial hypertension

In case 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 give specific advice on the continuation of growth hormone treatment in patients with resolved intracranial hypertension. However, clinical experience has shown that rein stitution of the therapy is often possible without recurrence of the intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Paediatric population

Prader-Willi syndrome

In patients with PWS, treatment should always be in combination with a calorie-restricted diet.

There have been reports of fatalities associated with the use of growth hormone in paediatric patients with PWS who had one or more of the following risk factors: severe obesity, history of respiratory impairment, sleep apnoea or unidentified respiratory infection. Patients with PWS and one or more of these risk factors may be at greater risk.

Patients with PWS should be evaluated for upper airway obstruction, sleep apnoea or respiratory infections before initiation of treatment with somatropin. In case of signs of upper airway obstruction, the problem should be solved by a specialist before starting treatment with somatropin.

Sleep apnoea should be assessed before onset of growth hormone treatment by recognized methods such as polysomnography or overnight oxymetry, and monitored if sleep apnoea is suspected.

If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted, and a new ENT assessment performed.

All patients with PWS should be evaluated for sleep apnoea and monitored if sleep apnoea is suspected.

All patients with PWS should be monitored for signs of respiratory infections which should be diagnosed as early as possible and treated aggressively.

All patients with PWS should have effective weight control before and during treatment with somatropin.

Scoliosis is common in patients with PWS. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis. Experience with long term treatment in adults and in patie nts with PWS is limited.

Small for gestational age

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

In SGA children/adolescents it is recommended to measure fasting 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.

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

Experience in initiating treatment in SGA patients near onset of puberty is l imited. It is therefore not recommended to initiate treatment near onset of puberty. Experience in patients with Silver-Russell syndrome is limited.

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

Acute critical illness

The effects of somatropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg somatropin daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with somatropin. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.
In all patients developing other or similar acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

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

4.5 Interaction with other medicinal products and other forms of interaction

Data from an interaction study performed in growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown. Also see section 4.4 for statements regarding diabetes mellitus and thyroid disorder and section 4.2 for statement on oral oestrogen replacement therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

For Omnitrope no clinical data on exposed pregnancies are available. Animal experimental data on reproductive toxicity of Omnitrope are not available. Treatment with Omnitrope should be nterrupted if pregnancy occurs.

During normal pregnancy levels of pituitary growth hormone fall markedly after 20 gestation weeks, being replaced almost entirely by placental growth hormone by 30 weeks. In view of this, it is unlikely that continued replacement therapy with somatropin would be necessary in growth hormone deficient women in the third trimester of pregnancy.

Breastfeeding

It is not known if somatropin is excreted into breast milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely.

Caution should be exercised when Omnitrope is administered to breast-feeding women.

Fertility

Fertility studies with Omnitrope have not been performed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients adverse effects related to fluid ret ention, such as peripheral oedema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common. In general these adverse effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose-reduction.

The incidence of these adverse effects is related to the administered dose, the age of patients, and possibly inversely related to the age of patients at the onset of growth hormone deficiency. In children such adverse effects are uncommon.

Omnitrope has given rise to the formation of antibodies in approximately 1 % of the patients. The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation, see section 4.4.

The following undesirable effects have been observed and reported during treatment with Omnitrope

with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Very rare: Leukemia*

Immune system disorders:

Common: Formation of antibodies

Endocrine disorders:

Rare: Diabetes mellitus type II

Nervous system disorders:

Common: In adults: paraesthesia

Uncommon: In adults: carpal tunnel syndrome. In children: paraesthesia

Rare: Benign intracranial hypertension

Skin and subcutaneous tissue disorders:

Common: In children: transient local skin reactions

Musculoskeletal and connective tissue disorders:

Common: In adults: stiffness in the extremities, arthralgia, myalgia

Uncommon: In children: stiffness in the extremities, arthralgia, myalgia

General disorders and administration site conditions:

Common: In adults: peripheral oedema

Uncommon: In children: peripheral oedema

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increased hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of therapy.

*Very rare cases of leukemia have been reported in growth hormone deficient children treated with Omnitrope, but the incidence appears to be similar to that in children without growth hormone deficiency, see section 4.4.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia.

Long-term overdose could result in signs and symptoms consistent with the known effects of human

growth hormone excess.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, anterior pituitary lobe hormones and analogues, ATC code: H01AC01.

Mechanism of action

Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores. Serum concentrations of IGF-I (Insulin-like Growth Factor-I) and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated.

Pharmacodynamic effects

Lipid metabolism

Somatropin induces hepatic LDL cholesterol receptors, and affects the profile of serum lipids and lipoproteins. In general, administration of somatropin to growth hormone deficient patients results in reduction in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.

Carbohydrate metabolism
Somatropin increases insulin but fasting blood glucose is commonly unchanged. Children with hypopituitarism may experience fasting hypoglycaemia. This condition is reversed by somatropin.

Water and mineral metabolism
Growth hormone deficiency is associated with decreased plasma and extracellular volumes. Both are rapidly increased after treatment with somatropin. Somatropin induces the retention of sodium, potassium and phosphorus.

Bone metabolism
Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopoenia results in an increase in bone mineral content and density at weight-bearing sites.

Physical capacity
Muscle strength and physical exercise capacity are improved after long-term treatment with somatropin. Somatropin also increases cardiac output, but the mechanism has yet to be clarified. A

decrease in peripheral vascular resistance may contribute to this effect.

Clinical efficacy and safety

In clinical trials in short children/adolescents born SGA doses of 0.033 and 0.067mg somatropin/kg body weight per day have been used for treatment until final height is reached. In 56 patients who are continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033mg/kg body weight per day) and +2.19 SDS (0.067mg/kg body eight per day). Literature data from untreated SGA children/adolescents without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of subcutaneously administered somatropin is approximately 80% in both healthy subjects and growth hormone deficient patients. A subcutaneous dose of 5 mg of Omnitrope powder and solvent for solution for injection in healthy adults results in plasma Cmax values of 71± 24 μg/l (mean± SD) and median tmax valueof 4 hours (range 2-8 hours), respectively.

Elimination
The mean terminal half-life of somatropin after intravenous administration in growth hormone deficient adults is about 0.4 hours. However, after subcutaneous administration of Omnitrope powder and solvent for solution for injection, a half-life of 3hours is achieved. The observed difference is likely due to slow absorption from the injection site following subcutaneous administration.

Special populations
The absolute bioavailability of somatropin seems to be similar in males and females following subcutaneous administration. Information about the pharmacokinetics of somatropin in geriatric and paediatric populations, in different races and in patients with renal, hepatic or cardiac insufficiency is either lacking or incomplete.

5.3 Preclinical safety data

In studies with Omnitrope regarding subacute toxicity and local tolerance, no clinically relevant effects have been observed.

In other studies with somatropin regarding general toxicity, local tolerance and reproduction toxicity no clinically relevant effects have been observed.

With somatropins, in vitro and in vivo genotoxicity studies on gene mutations and induction of chromosome aberrations have been negative.

An increased chromosome fragility has been observed in one in vitro study on lymphocytes taken from patients after long term treatment with somatropin and following the addition of the radiomimetic medicinal product bleomycin. The clinical ignificance of this finding is unclear.

In another study with somatropin, no increase in chromosomal abnormalities was found in the lymphocytes of patients who had received long-term somatropin therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
glycine
disodium hydrogen phosphate heptahydrate
sodium dihydrogen phosphate dihydrate
Solvent:
water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

Shelf life after reconstitution
After reconstitution, from a microbiological point of view, an immed iate use is recommended. However, the in -use stability has been demonstrated for up to 24 hours at 2°C - 8°C, in the original Package . Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

6.4 Special precautions for storage

Unopened vial
Store and transport refrigerated (2°C- 8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions of the in-use medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a stopper (fluor-resin laminated butyl rubber), a strip (aluminium) and a cap(violet polypropylene flip-off), and 1 ml of solvent in a vial (type I glass) with a stopper (fluor-resin laminated chlorobutyl elastomer), a strip (lacquered aluminium) and a cap (white polypropylene flip-off). Pack sizeof 1.

6.6 Special precautions for disposal and other handling

Omnitrope 1.3 mg/ml is supplied in a vial containing the active substance as a powder and the solvent filled in a vial for single use. Each vial must be reconstituted with the accompanying solvent only. The reconstituted solution should be administered using sterile, disposable syringes.

The following is a general description of the reconstitution and administration process. Reconstitution should be performed in accordance with good practice rules, particularly in the respect of asepsis.

1. Hands should be washed.

2. Flip off the plastic protective caps from the vials.

3. The top of the vials should be wiped with an antiseptic solution to prevent contamination of thecontents.

4. Use a sterile, disposable syringe (e.g. 2ml syringe) and needle (e.g. 0.33 mm x 12.7 mm) to withdraw all the solvent from the vial.

5. Take the vial with the powder, push the needle through the rubber closure and inject the solvent slowly into the vial aiming the stream of liquid against the glass wall in order to avoid foam.

6. Gently swirl the vial a few times until the content is completely dissolved. Do not shake; this may cause denaturation of the active substance.

7. If the solution is cloudy or contains particulate matter, it should not be used. The content must be clear and colourless after reconstitution.

8. Turn the vial upside down and using another sterile, disposable syringe of appropriate size (e.g.1 ml syringe) and injection needle (e.g. 0.25 mm x 8mm) withdraw a bit more than the doseneeded back into the syringe. Remove any air bubbles from the syringe. Bring the syringe to the correct dose needed.

9. Clean the injection site with an alcohol swab and administer Omnitrope by subcutaneous injection.

The solution is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISAT ION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER

EU/1/06/332/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 April 2006
Date of latest renewal: 12 April 2011