ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 2 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial delivers 2 mg of somatropin* (corresponding to 6 IU).

After reconstitution, 0.2 mL of suspension contains 2 mg somatropin (10 mg/mL).

*produced in Saccharomyces cerevisiae by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

White or almost white powder. The solvent is a clear, oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency (GHD).

Adult-onset: Patients with GHD in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one additional known deficiency of a pituitary hormone excluding prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a GHD.
Childhood-onset: In patients with childhood-onset isolated GHD (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be performed after completion of growth, except for those having low insulin-like growth factor-I (IGF-I) concentrations (< -2 standard deviation score (SDS)), 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

Diagnosis and therapy with this medicinal product should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with GHD.

Posology

Somatropin Biopartners should be administered subcutaneously at a concentration of 10 mg/mL.

Starting dose
Generally, 2 mg once a week for all patients apart from female patients receiving oral oestrogen therapy who should receive 3 mg once a week. In older or overweight patients, lower doses may be necessary.

Gender	**Starting dose**
Male	2 mg (6 IU)
Female (not on oral oestrogen)	2 mg (6 IU)
Female (on oral oestrogen)	3 mg (9 IU)

Dose adjustment
Initially, patients should have their IGF-I levels assessed at 3- to 4-weekly intervals until IGF-I SDS is in the target range of -0.5 to +1.5. Samples should be drawn 4 days after the previous dose (Day 4). Repeated adjustments in dose may be required, dependent on patients' IGF-I response. IGF-I levels should be acted upon, as indicated below.

IGF-I SDS	**Action on previous dose**	**Dose change at a time**
IGF-I SDS lower than -1	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and less than 1SDS increase from Baseline	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and more than 1 SDS increase from Baseline	Maintain	None
IGF-I SDS in the range of +1 to +2	Maintain or decrease depending on clinical status	None or -0.5 mg (all patients)
IGF-I SDS greater than +2	Decrease	-0.5 mg (all patients)

IGF-I = insulin-like growth factor-I, SDS = standard deviation score.

Conversion from required dose to injection volume and vial strength

Somatropin dose (mg)	**vials and solvent required for preparation of one dose***	**Injection volume (mL)**
1	one 2-mg vial reconstituted with 0.4 mL solvent	0.1
1.5		0.15
2		0.2

* Each vial contains an overfill of somatropin powder to allow the withdrawal of the required amount of somatropin when reconstituted (see section 6.6).

For other doses vials with 4 or 7 mg somatropin are available.

The minimum effective dose should be used. The treatment goal should be IGF-I concentrations within -0.5 and +1.5 SDS of the age corrected mean.

In order to reach the defined treatment goal, men may need lower growth hormone doses than women. Oral oestrogen administration increases the dose requirements in women. An increasing sensitivity to growth hormone (expressed as change in IGF-I per growth hormone dose) over time may be observed, particularly in men. The accuracy of the growth hormone dose should therefore be controlled every 6 months.

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.

The dose may be reduced in steps of 0.5 mg at a time. If the symptoms leading to the dose reduction disappear, at the judgment of the physician, the dose may be maintained at the decreased level or increased according to the dose adjustment scheme described above. If the symptom reappears after the dose increase, then the dose should be maintained at the previous lower dose.

Special populations

Older people
Experience with somatropin treatment in patients above 60 years of age is limited. Dose requirements may decline with increasing age.

Renal/hepatic impairment
No information in patients with renal or hepatic impairment is available and particular dose recommendations cannot be given.

Paediatric population
There is no relevant use of Somatropin Biopartners 2 mg in the paediatric population in the indication of long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone. For the treatment of children and adolescents aged 2 to 18 years the 10 mg and 20 mg vials of this medicinal product should be used.

Method of administration

The patient or carer should receive training to ensure understanding of the administration procedure before being allowed to (self-) inject.

Somatropin Biopartners is administered subcutaneously once a week. After reconstitution the injection should be administered immediately.

The subcutaneous injection should always be administered at the same time of the day to increase compliance and the site of injection must be varied to prevent lipoatrophy.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Somatropin must not be used when there is any evidence of tumour activity. Intracranial tumours must be inactive and antitumour therapy must be completed prior to the initiation of growth hormone therapy. Treatment should be discontinued if there is evidence of tumour (re)growth.
- Somatropin treatment must not be started in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure or similar conditions.

4.4 Special warnings and precautions for use

Malignancies

Patients with prior malignancies should be examined routinely for progression or recurrence.

Benign intracranial hypertension

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.

Insulin sensitivity

Because human growth hormone (hGH) may induce a state of insulin resistance and hyperglycaemia, patients treated with this medicinal product should be monitored for evidence of glucose intolerance. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin treatment is initiated. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Hypothyroidism may develop in patients with central subclinical hypothyroidism after initiating therapy with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to somatropin.
In patients with hypopituitarism receiving thyroxin replacement therapy, hyperpituitarism may develop. Thyroid function should therefore be closely monitored in all patients.

Adrenal function

Treatment with growth hormone may facilitate the development of adrenal insufficiency and potentially fatal adrenal crises in patients with organic GHD or idiopathic panhypopituitarism. It is therefore crucial to assess baseline and stress doses of glucocorticoids which may need to be adjusted when growth hormone therapy is initiated.

Adults with childhood-onset of GHD

Young adult patients with closed epiphyses who have previously been treated as children for GHD should be re-evaluated for GHD using the criteria for adult patients (see section 4.1) before replacement therapy is commenced at the doses recommended for adults.

Other precautions

This medicinal product is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy 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.

After accidental intramuscular injection, hypoglycaemia may occur.

Antibodies

Some patients may develop antibodies to this medicinal product. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy can inhibit the actions of hGH. Patients receiving concomitant glucocorticoid therapy should have their dose carefully adjusted.
Growth hormone increases the extrathyroidal conversion of thyroxin (T4) to triiodothyronine (T3) and may unmask central hypothyroidism. Thyroxine replacement therapy may therefore need to be initiated or adjusted.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.
In women taking oral oestrogens, a higher dose of somatropin may be required to achieve the treatment goal, see section 4.2.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. Because hGH may induce a state of insulin resistance, an adjustment of the insulin dose may be required.

Somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Somatropin Biopartners is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of this medicinal product in pregnant women. Very limited data on exposure to other somatropin preparations during early pregnancy did not indicate an adverse pregnancy outcome. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
During normal pregnancy, levels of pituitary growth hormone fall markedly after 20 weeks of gestation, 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. Somatropin Biopartners is not recommended during pregnancy.

Breast-feeding

No clinical studies have been conducted with Somatropin Biopartners in breast-feeding women. It is unknown whether somatropin or its metabolites are excreted in human breast milk; however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Caution should be exercised when this medicinal product is administered to breast-feeding women.

Fertility

Animal studies with other somatropin formulations have shown adverse effects but the available nonclinical data are considered insufficient to draw firm conclusions on the use in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Somatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials included approximately 530 patients treated with Somatropin Biopartners. When adverse reactions occurred, they tended to be transient and severity was generally mild to moderate. The safety profile of Somatropin Biopartners is generally consistent with the well known safety profile of daily growth hormone treatments. The adverse reactions most commonly reported were injection site related reactions, peripheral oedema, headache, myalgia, arthralgia, paraesthesia, hypothyroidism and decreased free thyroxine.

Tabulated list of adverse reactions

The following adverse reactions have been observed under treatment with Somatropin Biopartners in a 6-month controlled clinical study with 151 adult patients with GHD of adult- or childhood-onset and in a 6-month extension study. Additional reports based on published information for daily growth hormone treatments are listed with asterisks.
The frequency of adverse reactions listed below is defined using the following convention: 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), not known (cannot be estimated from the available data).

Infections and infestations
Common: Herpes simplex

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Neoplasm progression (1 case of neoplasm progression in a female patient with a history of neurofibromatosis and radiation treatment), acrochordon, craniopharyngioma

Blood and the lymphatic system disorders
Common: Decreased or increased white blood cell count, increased glycosylated haemoglobin, decreased haemoglobin

Immune system disorders
Common: Formation of antibodies against growth hormone

Endocrine disorders
Common: Adrenal insufficiency, decreased free thyroxine, decreased free tri-iodothyronine, increased blood TSH, hypothyroidism*

Metabolism and nutrition disorders
Very common: Mild hyperglycaemia*
Common: Impaired fasting glucose, hyperlipidaemia, increased blood insulin, increased blood cholesterol, decreased blood sodium, increased blood triglycerides, increased blood glucose, increased or decreased HDL, increased LDL
Not known: Insulin resistance*

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Headache
Common: Paraesthesia, hypoaesthesia, carpal tunnel syndrome, dizziness, somnolence
Rare: Benign intracranial hypertension*

Eye disorders
Common: Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Common: Tachycardia, heart rate abnormal/irregular

Vascular disorders
Common: Hypertension,increased blood pressure

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis

Gastrointestinal disorders
Common: Nausea

Hepatobiliary disorders
Common: Hyperbilirubinaemia, cholecystitis, liver test abnormal

Skin and subcutaneous tissue disorders
Common: Swelling face, acne, allergic dermatitis, hyperhidrosis, urticaria, rash

Musculoskeletal and connective tissue disorders
Common: Back pain, pain in extremities, arthralgia, shoulder pain, musculoskeletal stiffness, bone pain, muscular weakness, sensation of heaviness, tendonitis, joint swelling, arthritis, musculosceletal pain, myalgia*

Renal and urinary disorders
Common: Haematuria, increased blood uric acid, increased blood creatinine

Reproductive system and breast disorders
Common: Nipple pain
Uncommon: Gynaecomastia*

General disorders and administration site conditions
Very common: Oedema peripheral, oedema (local and generalised)*
Common: Fatigue, pain, asthenia, face oedema, local swelling, oedema, thirst, malaise, chest pain, increased weight, injection site pain

Investigations
Common: Increased blood phosphorus, increased or decreased IGF

Description of selected adverse reactions

Immunogenicity
Some patients may develop antibodies to rhGH. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

With regard to antibodies against host cell proteins, low anti-S. cerevisiae protein antibody titres similar to levels in the normal untreated population were found in some patients treated with this medicinal product. The generation of such antibodies with low binding activity is unlikely to be clinically relevant.

Malignancies/tumours
Cases of malignant and benign tumour recurrences, de-novo and secondary tumours have been reported in temporal relationship with somatropin therapy.

Paediatric population

With the exception of injection site related reactions and the formation of antibodies to rhGH which were reported more frequently in children than in adults the safety profile of Somatropin Biopartners is similar for children and adults.

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Due to the prolonged-release characteristics of this medicinal product peak levels of growth hormone can be expected approximately 15 hours after injection, see section 5.2. Long term over-dosing could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of hGH excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and agonists, ATC code: H01AC01

The somatropin in this medicinal product 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 active substance is identical to that of hGH of pituitary origin. The somatropin in this medicinal product is synthesised in yeast (*Saccharomyces cerevisiae*).

Mechanism of action

The biological effects of somatropin are equivalent to those of hGH of pituitary origin.

Somatropin promotes cellular protein synthesis and nitrogen retention. The most prominent effect of somatropin in children is the stimulation of the growth plates of long bones.

Pharmacodynamic effects

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in patients with -GHD, 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.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical efficacy and safety

Safety and efficacy in adults with GHD was assessed in a phase III, double-blind, randomized, placebo-controlled, parallel-group, multicentre study. This pivotal phase III study comprised 151 adult patients with GHD of adult- or childhood-onset and lasted 6 months. After 6 months of weekly treatment with Somatropin Biopartners, there was a statistically significant reduction of 1.6 kg in fat mass in the Somatropin Biopartners group compared to the placebo group. A similar improvement was observed for the secondary efficacy endpoints namely increase in lean body mass, serum IGF-I and IGF-I SDS. Effects were maintained throughout the 6-month follow-up period.

5.2 Pharmacokinetic properties

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 4.4 mg prolonged release somatropin to adults with GHD the C_{max} and t_{max} of plasma hGH were about 4.5 ng/mL and 15 h respectively. The apparent terminal half-life was about 16.8 h in adults, presumably reflecting slow absorption from the site of injection.
The t_{max} was later and the half-life longer following the administration of Somatropin Biopartners than when immediate release products had been previously administered once daily to the same subjects reflecting the slower and more prolonged release of hGH from the site of injection of Somatropin Biopartners.

Distribution

No accumulation of hGH following multiple dosing of this medicinal product has been observed.

Biotransformation / Elimination

The metabolic fate of hGH involves classical protein catabolism in both the liver and kidney.

5.3 Preclinical safety data

Non-clinical pharmacokinetic and pharmacodynamic studies in dogs and juvenile monkeys showed that Somatropin Biopartners released recombinant hGH in a prolonged manner and increased serum IGF-I for an extended period up to 5-6 days.

Non-clinical data revealed no specific hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

Long term carcinogenicity studies with Somatropin Biopartners have not been conducted. There are no specific studies which address local tolerance in animals after subcutaneous injection, but data available from the repeated-dose toxicity studies revealed swelling and inflammatory infiltrate at the injection sites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium hyaluronate
Egg phospholipids
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous.

Solvent:
Medium chain triglycerides.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution: From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder: Vial (type I glass) closed with a rubber stopper (butyl) and a yellow flip-off cap (aluminium and plastic).
Solvent: Vial (Type I glass) closed with a rubber stopper (butyl) and a flip-off cap (aluminium and plastic).

Each vial of powder delivers 2 mg somatropin; each vial of solvent contains 1.5 mL liquid.
Pack size: 4 vials of powder and 4 vials of solvent.

6.6 Special precautions for disposal and other handling

Reconstitution

Somatropin Biopartners 2 mg should be reconstituted with 0.4 mL solvent.

The suspension should appear uniform and white.

The vial contains an overfill of somatropin powder to allow the withdrawal of up to 2 mg (0.2 mL suspension) of somatropin when reconstituted.

Each vial is for single use only.

Reconstitution and dilution should be performed using aseptic techniques to ensure the sterility of the prepared suspension. The solvent vial should be warmed to room temperature and the powder vial should be tapped and shaken to ensure the powder is moving freely. After removal of the protective caps from the top of both vials the rubber stoppers should be cleaned with an alcohol swab. A 1 mL graduated syringe with 19 Gauge or wider needle should be used for withdrawing the solvent from its

vial. The syringe should be filled with a volume of air equal to the required volume of the solvent for injection and the air injected into the solvent vial to make it easier to withdraw the solvent. The vial should be turned upside down, with the syringe in and the tip of the needle should be placed in the solvent. To remove any bubbles, the syringe should be tapped gently. The plunger should be pushed up gently, until all bubbles are removed from the syringe and needle. The syringe should be filled with the correct volume of the solvent for injection as listed above and the syringe needle withdrawn from the vial subsequently. Any remaining solvent should not be used for a second preparation.

Holding the needle against the inside vial wall, the entire contents of the syringe should be injected into the powder vial. Without touching the rubber top the vial should be swirled vigorously until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. The swirling should only be stopped once the suspension appears uniform, white and all the powder on the bottom is dispersed. After reconstitution the medicinal product should be used immediately before the suspension settles. If not used immediately, the suspension must be reconstituted again by swirling immediately before injection. The appropriate volume should be withdrawn in a sterile syringe via a sterile 26-gauge needle: The vial should be turned upside down, with the syringe in, and the tip of the needle should be placed in the suspension which is then slowly withdrawn. To remove small air bubbles the syringe should be tapped gently. The powder should be homogenously suspended in the injection vehicle prior to administration. The syringe should be held upright and gentle pressure applied to the plunger until a small drop of suspension appears at the end of the needle. The injection site should be cleaned with an alcohol swab and the suspension injected over a period of 5 seconds.

Detailed information on how to administer this medicinal product is provided in section 3 of the patient leaflet.

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)

EU/1/13/849/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 4 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial delivers 4 mg of somatropin* (corresponding to 12 IU)

After reconstitution, 0.4 mL of suspension contains 4 mg somatropin (10 mg/mL).

*produced in Saccharomyces cerevisiae by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

White or almost white powder. The solvent is a clear, oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency (GHD).

Adult-onset: Patients with GHD in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one additional known deficiency of a pituitary hormone excluding prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a GHD.
Childhood-onset: In patients with childhood-onset isolated GHD (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be performed after completion of growth, except for those having low insulin-like growth factor-I (IGF-I) concentrations (< -2 standard deviation score (SDS)), 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

Diagnosis and therapy with this medicinal product should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with GHD.

Posology

Somatropin Biopartners should be administered subcutaneously at a concentration of 10 mg/mL.

Starting dose
Generally, 2 mg once a week for all patients apart from female patients receiving oral oestrogen therapy who should receive 3 mg once a week. In older or overweight patients, lower doses may be necessary.

Gender	**Starting dose**
Male	2 mg (6 IU)
Female (not on oral oestrogen)	2 mg (6 IU)
Female (on oral oestrogen)	3 mg (9 IU)

Dose adjustment
Initially, patients should have their IGF-I levels assessed at 3- to 4-weekly intervals until IGF-I SDS is in the target range of -0.5 to +1.5. Samples should be drawn 4 days after the previous dose (Day 4). Repeated adjustments in dose may be required, dependent on patients' IGF-I response. IGF-I levels should be acted upon, as indicated below.

IGF-I SDS	**Action on previous dose**	**Dose change at a time**
IGF-I SDS lower than -1	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and less than 1SDS increase from Baseline	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and more than 1 SDS increase from Baseline	Maintain	None
IGF-I SDS in the range of +1 to +2	Maintain or decrease depending on clinical status	None or -0.5 mg (all patients)
IGF-I SDS greater than +2	Decrease	-0.5 mg (all patients)

IGF-I = insulin-like growth factor-I, SDS = standard deviation score.

Conversion from required dose to injection volume and vial strength

Somatropin dose (mg)	**vials and solvent required for preparation of one dose***	**Injection volume (mL)**
2.5	one 4-mg vial reconstituted with 0.6 mL solvent	0.25
3		0.3
3.5		0.35
4		0.4

* Each vial contains an overfill of somatropin powder to allow the withdrawal of the required amount of somatropin when reconstituted (see section 6.6).

For other doses vials with 2 or 7 mg somatropin are available.

The minimum effective dose should be used. The treatment goal should be IGF-I concentrations within -0.5 and +1.5 SDS of the age corrected mean.

In order to reach the defined treatment goal, men may need lower growth hormone doses than women. Oral oestrogen administration increases the dose requirements in women. An increasing sensitivity to growth hormone (expressed as change in IGF-I per growth hormone dose) over time may be observed, particularly in men. The accuracy of the growth hormone dose should therefore be controlled every 6 months.

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.

The dose may be reduced in steps of 0.5 mg at a time. If the symptoms leading to the dose reduction disappear, at the judgment of the physician, the dose may be maintained at the decreased level or increased according to the dose adjustment scheme described above. If the symptom reappears after the dose increase, then the dose should be maintained at the previous lower dose.

Special populations

Older people
Experience with somatropin treatment in patients above 60 years of age is limited. Dose requirements may decline with increasing age.

Renal/hepatic impairment
No information in patients with renal or hepatic impairment is available and particular dose recommendations cannot be given.

Paediatric population
There is no relevant use of Somatropin Biopartners 4 mg in the paediatric population in the indication of long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone. For the treatment of children and adolescents aged 2 to 18 years the 10 mg and 20 mg vials of this medicinal product should be used.

Method of administration

The patient or carer should receive training to ensure understanding of the administration procedure before being allowed to (self-) inject.

Somatropin Biopartners is administered subcutaneously once a week. After reconstitution the injection should be administered immediately.

The subcutaneous injection should always be administered at the same time of the day to increase compliance and the site of injection must be varied to prevent lipoatrophy.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Somatropin must not be used when there is any evidence of tumour activity. Intracranial tumours must be inactive and antitumour therapy must be completed prior to the initiation of growth hormone therapy. Treatment should be discontinued if there is evidence of tumour re)growth.
- Somatropin treatment must not be started in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure or similar conditions.

4.4 Special warnings and precautions for use

Malignancies

Patients with prior malignancies should be examined routinely for progression or recurrence.

Benign intracranial hypertension

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.

Insulin sensitivity

Because human growth hormone (hGH) may induce a state of insulin resistance and hyperglycaemia, patients treated with this medicinal product should be monitored for evidence of glucose intolerance. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin treatment is initiated. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Hypothyroidism may develop in patients with central subclinical hypothyroidism after initiating therapy with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to somatropin.
In patients with hypopituitarism receiving thyroxin replacement therapy, hyperpituitarism may develop. Thyroid function should therefore be closely monitored in all patients.

Adrenal function

Treatment with growth hormone may facilitate the development of adrenal insufficiency and potentially fatal adrenal crises in patients with organic GHD or idiopathic panhypopituitarism. It is therefore crucial to assess baseline and stress doses of glucocorticoids which may need to be adjusted when growth hormone therapy is initiated.

Adults with childhood-onset of GHD

Young adult patients with closed epiphyses who have previously been treated as children for GHD should be re-evaluated for GHD using the criteria for adult patients (see section 4.1) before replacement therapy is commenced at the doses recommended for adults.

Other precautions

This medicinal product is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy 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.

After accidental intramuscular injection, hypoglycaemia may occur.

Antibodies

Some patients may develop antibodies to this medicinal product. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy can inhibit the actions of hGH. Patients receiving concomitant glucocorticoid therapy should have their dose carefully adjusted.
Growth hormone increases the extrathyroidal conversion of thyroxin (T4) to triiodothyronine (T3) and may unmask central hypothyroidism. Thyroxine replacement therapy may therefore need to be initiated or adjusted.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.
In women taking oral oestrogens, a higher dose of somatropin may be required to achieve the treatment goal, see section 4.2.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. Because hGH may induce a state of insulin resistance, an adjustment of the insulin dose may be required.

Somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Somatropin Biopartners is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of this medicinal product in pregnant women. Very limited data on exposure to other somatropin preparations during early pregnancy did not indicate an adverse pregnancy outcome. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
During normal pregnancy, levels of pituitary growth hormone fall markedly after 20 weeks of gestation, 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. Somatropin Biopartners is not recommended during pregnancy.

Breast-feeding

No clinical studies have been conducted with Somatropin Biopartners in breast-feeding women. It is unknown whether somatropin or its metabolites are excreted in human breast milk; however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Caution should be exercised when this medicinal product is administered to breast-feeding women.

Fertility

Animal studies with other somatropin formulations have shown adverse effects but the available nonclinical data are considered insufficient to draw firm conclusions on the use in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Somatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials included approximately 530 patients treated with Somatropin Biopartners. When adverse reactions occurred, they tended to be transient and severity was generally mild to moderate. The safety profile of Somatropin Biopartners is generally consistent with the well known safety profile of daily growth hormone treatments. The adverse reactions most commonly reported were injection site related reactions, peripheral oedema, headache, myalgia, arthralgia, paraesthesia, hypothyroidism and decreased free thyroxine.

Tabulated list of adverse reactions

The following adverse reactions have been observed under treatment with Somatropin Biopartners in a 6-month controlled clinical study with 151 adult patients with GHD of adult- or childhood-onset and in a 6-month extension study. Additional reports based on published information for daily growth hormone treatments are listed with asterisks.
The frequency of adverse reactions listed below is defined using the following convention: 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), not known (cannot be estimated from the available data):

Infections and infestations
Common: Herpes simplex

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Neoplasm progression (1 case of neoplasm progression in a female patient with a history of neurofibromatosis and radiation treatment), acrochordon, craniopharyngioma

Blood and the lymphatic system disorders
Common: Decreased or increased white blood cell count, increased glycosylated haemoglobin, decreased haemoglobin

Immune system disorders
Common: Formation of antibodies against growth hormone

Endocrine disorders
Common: Adrenal insufficiency, decreased free thyroxine, decreased free tri-iodothyronine, increased blood TSH, hypothyroidism*

Metabolism and nutrition disorders

Very common: Mild hyperglycaemia*
Common: Impaired fasting glucose, hyperlipidaemia, increased blood insulin, increased blood cholesterol, decreased blood sodium, increased blood triglycerides, increased blood glucose, increased or decreased HDL, increased LDL
Not known: Insulin resistance*

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Headache
Common: Paraesthesia, hypoaesthesia, carpal tunnel syndrome, dizziness, somnolence
Rare: Benign intracranial hypertension*

Eye disorders
Common: Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Common: Tachycardia, heart rate abnormal/irregular

Vascular disorders
Common: Hypertension,increased blood pressure

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis

Gastrointestinal disorders
Common: Nausea

Hepatobiliary disorders
Common: Hyperbilirubinaemia, cholecystitis, liver test abnormal

Skin and subcutaneous tissue disorders
Common: Swelling face, acne, allergic dermatitis, hyperhidrosis, urticaria, rash

Musculoskeletal and connective tissue disorders
Common: Back pain, pain in extremities, arthralgia, shoulder pain, musculoskeletal stiffness, bone pain, muscular weakness, sensation of heaviness, tendonitis, joint swelling, arthritis, musculosceletal pain, myalgia*

Renal and urinary disorders
Common: Haematuria, increased blood uric acid, increased blood creatinine

Reproductive system and breast disorders
Common: Nipple pain
Uncommon: Gynaecomastia*

General disorders and administration site conditions
Very common: Oedema peripheral, oedema (local and generalised)*
Common: Fatigue, pain, asthenia, face oedema, local swelling, oedema, thirst, malaise, chest pain, increased weight, injection site pain

Investigations
Common: Increased blood phosphorus, increased or decreased IGF

Description of selected adverse reactions

Immunogenicity
Some patients may develop antibodies to rhGH. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

With regard to antibodies against host cell proteins, low anti-S. cerevisiae protein antibody titres similar to levels in the normal untreated population were found in some patients treated with this medicinal product. The generation of such antibodies with low binding activity is unlikely to be clinically relevant.

Malignancies/tumours
Cases of malignant and benign tumour recurrences, de-novo and secondary tumours have been reported in temporal relationship with somatropin therapy.

Paediatric population

With the exception of injection site related reactions and the formation of antibodies to rhGH which were reported more frequently in children than in adults the safety profile of Somatropin Biopartners is similar for children and adults.

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Due to the prolonged-release characteristics of this medicinal product peak levels of growth hormone can be expected approximately 15 hours after injection, see section 5.2. Long term over-dosing could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of hGH excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and agonists, ATC code: H01AC01

The somatropin in this medicinal product 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 active substance is identical to that of hGH of pituitary origin. The somatropin in this medicinal product is synthesised in yeast (*Saccharomyces cerevisiae*).

Mechanism of action

The biological effects of somatropin are equivalent to those of hGH of pituitary origin.

Somatropin promotes cellular protein synthesis and nitrogen retention. The most prominent effect of somatropin in children is the stimulation of the growth plates of long bones.

Pharmacodynamic effects

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in patients with -GHD, 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.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical efficacy and safety

Safety and efficacy in adults with GHD was assessed in a phase III, double-blind, randomized, placebo-controlled, parallel-group, multicentre study. This pivotal phase III study comprised 151 adult patients with GHD of adult- or childhood-onset and lasted 6 months. After 6 months of weekly treatment with Somatropin Biopartners, there was a statistically significant reduction of 1.6 kg in fat mass in the Somatropin Biopartners group compared to the placebo group. A similar improvement was observed for the secondary efficacy endpoints namely increase in lean body mass, serum IGF-I and IGF-I SDS. Effects were maintained throughout the 6-month follow-up period.

5.2 Pharmacokinetic properties

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 4.4 mg prolonged release somatropin to adults with GHD the C_{max} and t_{max} of plasma hGH were about 4.5 ng/mL and 15 h respectively. The apparent terminal half-life was about 16.8 h in adults, presumably reflecting slow absorption from the site of injection.
The t_{max} was later and the half-life longer following the administration of Somatropin Biopartners than when immediate release products had been previously administered once daily to the same subjects reflecting the slower and more prolonged release of hGH from the site of injection of Somatropin Biopartners.

Distribution

No accumulation of hGH following multiple dosing of this medicinal product has been observed.

Biotransformation / Elimination

The metabolic fate of hGH involves classical protein catabolism in both the liver and kidney.

5.3 Preclinical safety data

Non-clinical pharmacokinetic and pharmacodynamic studies in dogs and juvenile monkeys showed that Somatropin Biopartners released recombinant hGH in a prolonged manner and increased serum IGF-I for an extended period up to 5-6 days.

Non-clinical data revealed no specific hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

Long term carcinogenicity studies with Somatropin Biopartners have not been conducted. There are no specific studies which address local tolerance in animals after subcutaneous injection, but data available from the repeated-dose toxicity studies revealed swelling and inflammatory infiltrate at the injection sites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium hyaluronate
Egg phospholipids
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous.

Solvent:
Medium chain triglycerides.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution: From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder: Vial (type I glass) closed with a rubber stopper (butyl) and a pink flip-off cap (aluminium and plastic).
Solvent: Vial (Type I glass) closed with a rubber stopper (butyl) and a flip-off cap (aluminium and plastic).

Each vial of powder delivers 4 mg somatropin; each vial of solvent contains 1.5 mL liquid.
Pack size: 4 vials of powder and 4 vials of solvent.

6.6 Special precautions for disposal and other handling

Reconstitution

Somatropin Biopartners 4 mg should be reconstituted with 0.6 mL solvent.

The suspension should appear uniform and white.

The vial contains an overfill of somatropin powder to allow the withdrawal of up to 4 mg (0.4 mL suspension) of somatropin when reconstituted.

Each vial is for single use only.

Reconstitution and dilution should be performed using aseptic techniques to ensure the sterility of the prepared suspension. The solvent vial should be warmed to room temperature and the powder vial should be tapped and shaken to ensure the powder is moving freely. After removal of the protective caps from the top of both vials the rubber stoppers should be cleaned with an alcohol swab. A 1 mL graduated syringe with 19 Gauge or wider needle should be used for withdrawing the solvent from its vial. The syringe should be filled with a volume of air equal to the required volume of the solvent for injection and the air injected into the solvent vial to make it easier to withdraw the solvent. The vial should be turned upside down, with the syringe in and the tip of the needle should be placed in the solvent. To remove any bubbles, the syringe should be tapped gently. The plunger should be pushed up gently, until all bubbles are removed from the syringe and needle. The syringe should be filled with the correct volume of the solvent for injection as listed above and the syringe needle withdrawn from the vial subsequently. Any remaining solvent should not be used for a second preparation.

Holding the needle against the inside vial wall, the entire contents of the syringe should be injected into the powder vial. Without touching the rubber top the vial should be swirled vigorously until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. The swirling should only be stopped once the suspension appears uniform, white and all the powder on the bottom is dispersed. After reconstitution the medicinal product should be used immediately before the suspension settles. If not used immediately, the suspension must be reconstituted again by swirling immediately before injection. The appropriate volume should be withdrawn in a sterile syringe via a sterile 26-gauge needle: The vial should be turned upside down, with the syringe in, and the tip of the needle should be placed in the suspension which is then slowly withdrawn. To remove small air bubbles the syringe should be tapped gently. The powder should be homogenously suspended in the injection vehicle prior to administration. The syringe should be held upright and gentle pressure applied to the plunger until a small drop of suspension appears at the end of the needle. The injection site should be cleaned with an alcohol swab and the suspension injected over a period of 5 seconds.

Detailed information on how to administer this medicinal product is provided in section 3 of the patient leaflet.

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

7. MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany
Tel: +49 (0) 7121 948 7756
Fax:+49 (0) 7121 346 255
e-mail: info@biopartners.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 7 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial delivers 7 mg of somatropin* (corresponding to 21 IU)

After reconstitution, 0.7 mL of suspension contains 7 mg somatropin (10 mg/mL).

*produced in Saccharomyces cerevisiae by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

White or almost white powder. The solvent is a clear, oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency (GHD).

Adult-onset: Patients with GHD in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one additional known deficiency of a pituitary hormone excluding prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a GHD.
Childhood-onset: In patients with childhood-onset isolated GHD (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be performed after completion of growth, except for those having low insulin-like growth factor-I (IGF-I) concentrations (< -2 standard deviation score (SDS)), 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

Diagnosis and therapy with this medicinal product should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with GHD.

Posology

Somatropin Biopartners should be administered subcutaneously at a concentration of 10 mg/mL.

Starting dose
Generally, 2 mg once a week for all patients apart from female patients receiving oral oestrogen therapy who should receive 3 mg once a week. In older or overweight patients, lower doses may be necessary.

Gender	**Starting dose**
Male	2 mg (6 IU)
Female (not on oral oestrogen)	2 mg (6 IU)
Female (on oral oestrogen)	3 mg (9 IU)

Dose adjustment
Initially, patients should have their IGF-I levels assessed at 3- to 4-weekly intervals until IGF-I SDS is in the target range of -0.5 to +1.5. Samples should be drawn 4 days after the previous dose (Day 4). Repeated adjustments in dose may be required, dependent on patients' IGF-I response. IGF-I levels should be acted upon, as indicated below.

IGF-I SDS	**Action on previous dose**	**Dose change at a time**
IGF-I SDS lower than -1	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and less than 1SDS increase from Baseline	Increase	+1.5 mg (female on oral oestrogen) +1.0 mg (all other patients)
IGF-I SDS in the range of -1 to +1 and more than 1 SDS increase from Baseline	Maintain	None
IGF-I SDS in the range of +1 to +2	Maintain or decrease depending on clinical status	None or -0.5 mg (all patients)
IGF-I SDS greater than +2	Decrease	-0.5 mg (all patients)

IGF-I = insulin-like growth factor-I, SDS = standard deviation score.

Conversion from required dose to injection volume and vial strength

Somatropin dose (mg)	**vials and solvent required for preparation of one dose***	**Injection volume (mL)**
4.5	one 7-mg vial reconstituted with 0.9 mL solvent	0.45
5		0.5
5.5		0.55
6		0.6
6.5		0.65
7		0.7

* Each vial contains an overfill of somatropin powder to allow the withdrawal of the required amount of somatropin when reconstituted (see section 6.6).

For other doses vials with 2 or 4 mg somatropin are available.

The minimum effective dose should be used. The treatment goal should be IGF-I concentrations within -0.5 and +1.5 SDS of the age corrected mean.

In order to reach the defined treatment goal, men may need lower growth hormone doses than women. Oral oestrogen administration increases the dose requirements in women. An increasing sensitivity to growth hormone (expressed as change in IGF-I per growth hormone dose) over time may be observed, particularly in men. The accuracy of the growth hormone dose should therefore be controlled every 6 months.

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.

The dose may be reduced in steps of 0.5 mg at a time. If the symptoms leading to the dose reduction disappear, at the judgment of the physician, the dose may be maintained at the decreased level or increased according to the dose adjustment scheme described above. If the symptom reappears after the dose increase, then the dose should be maintained at the previous lower dose.

Special populations

Older people
Experience with somatropin treatment in patients above 60 years of age is limited. Dose requirements may decline with increasing age.

Renal/hepatic impairment
No information in patients with renal or hepatic impairment is available and particular dose recommendations cannot be given.

Paediatric population
There is no relevant use of Somatropin Biopartners 7 mg in the paediatric population in the indication of long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone. For the treatment of children and adolescents aged 2 to 18 years the 10 mg and 20 mg vials of this medicinal product should be used.

Method of administration

The patient or carer should receive training to ensure understanding of the administration procedure before being allowed to (self-) inject.

Somatropin Biopartners is administered subcutaneously once a week. After reconstitution the injection should be administered immediately.

The subcutaneous injection should always be administered at the same time of the day to increase compliance and the site of injection must be varied to prevent lipoatrophy.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Somatropin must not be used when there is any evidence of tumour activity. Intracranial tumours must be inactive and antitumour therapy must be completed prior to the initiation of growth hormone therapy. Treatment should be discontinued if there is evidence of tumour (re)growth.
- Somatropin treatment must not be started in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure or similar conditions.

4.4 Special warnings and precautions for use

Malignancies

Patients with prior malignancies should be examined routinely for progression or recurrence.

Benign intracranial hypertension

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.

Insulin sensitivity

Because human growth hormone (hGH) may induce a state of insulin resistance and hyperglycaemia, patients treated with this medicinal product should be monitored for evidence of glucose intolerance. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin treatment is initiated. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Hypothyroidism may develop in patients with central subclinical hypothyroidism after initiating therapy with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to somatropin.
In patients with hypopituitarism receiving thyroxin replacement therapy, hyperpituitarism may develop. Thyroid function should therefore be closely monitored in all patients.

Adrenal function

Treatment with growth hormone may facilitate the development of adrenal insufficiency and potentially fatal adrenal crises in patients with organic GHD or idiopathic panhypopituitarism. It is therefore crucial to assess baseline and stress doses of glucocorticoids which may need to be adjusted when growth hormone therapy is initiated.

Adults with childhood-onset of GHD

Young adult patients with closed epiphyses who have previously been treated as children for GHD should be re-evaluated for GHD using the criteria for adult patients (see section 4.1) before replacement therapy is commenced at the doses recommended for adults.

Other precautions

This medicinal product is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy 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.

After accidental intramuscular injection, hypoglycaemia may occur.

Antibodies

Some patients may develop antibodies to this medicinal product. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy can inhibit the actions of hGH. Patients receiving concomitant glucocorticoid therapy should have their dose carefully adjusted.
Growth hormone increases the extrathyroidal conversion of thyroxin (T4) to triiodothyronine (T3) and may unmask central hypothyroidism. Thyroxine replacement therapy may therefore need to be initiated or adjusted.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.
In women taking oral oestrogens, a higher dose of somatropin may be required to achieve the treatment goal, see section 4.2.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. Because hGH may induce a state of insulin resistance, an adjustment of the insulin dose may be required.

Somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Somatropin Biopartners is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of this medicinal product in pregnant women. Very limited data on exposure to other somatropin preparations during early pregnancy did not indicate an adverse pregnancy outcome. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
During normal pregnancy, levels of pituitary growth hormone fall markedly after 20 weeks of gestation, 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. Somatropin Biopartners is not recommended during pregnancy.

Breast-feeding

No clinical studies have been conducted with Somatropin Biopartners in breast-feeding women. It is unknown whether somatropin or its metabolites are excreted in human breast milk; however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Caution should be exercised when this medicinal product is administered to breast-feeding women.

Fertility

Animal studies with other somatropin formulations have shown adverse effects but the available nonclinical data are considered insufficient to draw firm conclusions on the use in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Somatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials included approximately 530 patients treated with Somatropin Biopartners. When adverse reactions occurred, they tended to be transient and severity was generally mild to moderate. The safety profile of Somatropin Biopartners is generally consistent with the well known safety profile of daily growth hormone treatments. The adverse reactions most commonly reported were injection site related reactions, peripheral oedema, headache, myalgia, arthralgia, paraesthesia, hypothyroidism and decreased free thyroxine.

Tabulated list of adverse reactions

The following adverse reactions have been observed under treatment with Somatropin Biopartners in a 6-month controlled clinical study with 151 adult patients with GHD of adult or childhood-onset and in a 6-month extension study. Additional reports based on published information for daily growth hormone treatments are listed with asterisks.
The frequency of adverse reactions listed below is defined using the following convention: 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), not known (cannot be estimated from the available data):

Infections and infestations
Common: Herpes simplex

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Neoplasm progression (1 case of neoplasm progression in a female patient with a history of neurofibromatosis and radiation treatment), acrochordon, craniopharyngioma

Blood and the lymphatic system disorders
Common: Decreased or increased white blood cell count, increased glycosylated haemoglobin, decreased haemoglobin

Immune system disorders
Common: Formation of antibodies against growth hormone

Endocrine disorders
Common: Adrenal insufficiency, decreased free thyroxine, decreased free tri-iodothyronine, increased blood TSH, hypothyroidism*

Metabolism and nutrition disorders
Very common: Mild hyperglycaemia*
Common: Impaired fasting glucose, hyperlipidaemia, increased blood insulin, increased blood cholesterol, decreased blood sodium, increased blood triglycerides, increased blood glucose, increased or decreased HDL, increased LDL
Not known: Insulin resistance*

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Headache
Common: Paraesthesia, hypoaesthesia, carpal tunnel syndrome, dizziness, somnolence
Rare: Benign intracranial hypertension*
Eye disorders
Common: Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Common: Tachycardia, heart rate abnormal/irregular

Vascular disorders
Common: Hypertension,increased blood pressure

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis

Gastrointestinal disorders
Common: Nausea

Hepatobiliary disorders
Common: Hyperbilirubinaemia, cholecystitis, liver test abnormal

Skin and subcutaneous tissue disorders
Common: Swelling face, acne, allergic dermatitis, hyperhidrosis, urticaria, rash

Musculoskeletal and connective tissue disorders
Common: Back pain, pain in extremities, arthralgia, shoulder pain, musculoskeletal stiffness, bone pain, muscular weakness, sensation of heaviness, tendonitis, joint swelling, arthritis, musculosceletal pain, myalgia*

Renal and urinary disorders
Common: Haematuria, increased blood uric acid, increased blood creatinine

Reproductive system and breast disorders
Common: Nipple pain
Uncommon: Gynaecomastia*

General disorders and administration site conditions
Very common: Oedema peripheral, oedema (local and generalised)*
Common: Fatigue, pain, asthenia, face oedema, local swelling, oedema, thirst, malaise, chest pain, increased weight, injection site pain

Investigations
Common: Increased blood phosphorus, increased or decreased IGF

Description of selected adverse reactions

Immunogenicity
Some patients may develop antibodies to rhGH. Somatropin Biopartners has given rise to the formation of antibodies in approximately 4% of adult patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.

With regard to antibodies against host cell proteins, low anti-S. cerevisiae protein antibody titres similar to levels in the normal untreated population were found in some patients treated with this medicinal product. The generation of such antibodies with low binding activity is unlikely to be clinically relevant.

Malignancies/tumours
Cases of malignant and benign tumour recurrences, de-novo and secondary tumours have been reported in temporal relationship with somatropin therapy.

Paediatric population

With the exception of injection site related reactions and the formation of antibodies to rhGH which were reported more frequently in children than in adults the safety profile of Somatropin Biopartners is similar for children and adults.

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Due to the prolonged-release characteristics of this medicinal product peak levels of growth hormone can be expected approximately 15 hours after injection, see section 5.2. Long term over-dosing could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of hGH excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and agonists, ATC code: H01AC01

The somatropin in this medicinal product 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 active substance is identical to that of hGH of pituitary origin. The somatropin in this medicinal product is synthesised in yeast (*Saccharomyces cerevisiae*).

Mechanism of action

The biological effects of somatropin are equivalent to those of hGH of pituitary origin.

Somatropin promotes cellular protein synthesis and nitrogen retention. The most prominent effect of somatropin in children is the stimulation of the growth plates of long bones.

Pharmacodynamic effects

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in patients with -GHD, 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.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical efficacy and safety

Safety and efficacy in adults with GHD was assessed in a phase III, double-blind, randomized, placebo-controlled, parallel-group, multicentre study. This pivotal phase III study comprised 151 adult patients with GHD of adult- or childhood-onset and lasted 6 months. After 6 months of weekly treatment with Somatropin Biopartners, there was a statistically significant reduction of 1.6 kg in fat mass in the Somatropin Biopartners group compared to the placebo group. A similar improvement was observed for the secondary efficacy endpoints namely increase in lean body mass, serum IGF-I and IGF-I SDS. Effects were maintained throughout the 6-month follow-up period.

5.2 Pharmacokinetic properties

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 4.4 mg prolonged release somatropin to adults with GHD the C_{max} and t_{max} of plasma hGH were about 4.5 ng/mL and 15 h respectively. The apparent terminal half-life was about 16.8 h in adults, presumably reflecting slow absorption from the site of injection.
The t_{max} was later and the half-life longer following the administration of Somatropin Biopartners than when immediate release products had been previously administered once daily to the same subjects reflecting the slower and more prolonged release of hGH from the site of injection of Somatropin Biopartners.

Distribution

No accumulation of hGH following multiple dosing of this medicinal product has been observed.

Biotransformation / Elimination

The metabolic fate of hGH involves classical protein catabolism in both the liver and kidney.

5.3 Preclinical safety data

Non-clinical pharmacokinetic and pharmacodynamic studies in dogs and juvenile monkeys showed that Somatropin Biopartners released recombinant hGH in a prolonged manner and increased serum IGF-I for an extended period up to 5-6 days.

Non-clinical data revealed no specific hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

Long term carcinogenicity studies with Somatropin Biopartners have not been conducted. There are no specific studies which address local tolerance in animals after subcutaneous injection, but data available from the repeated-dose toxicity studies revealed swelling and inflammatory infiltrate at the injection sites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium hyaluronate
Egg phospholipids
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous.

Solvent:
Medium chain triglycerides.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution: From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder: Vial (type I glass) closed with a rubber stopper (butyl) and a light-blue flip-off cap (aluminium and plastic).
Solvent: Vial (Type I glass) closed with a rubber stopper (butyl) and a flip-off cap (aluminium and plastic).

Each vial of powder delivers 7 mg somatropin; each vial of solvent contains 1.5 mL liquid.
Pack size: 4 vials of powder and 4 vials of solvent.

6.6 Special precautions for disposal and other handling

Reconstitution

Somatropin Biopartners 7 mg should be reconstituted with 0.9 mL solvent.

The suspension should appear uniform and white.

The vial contains an overfill of somatropin powder to allow the withdrawal of up to 7 mg (0.7 mL suspension) of somatropin when reconstituted.

Each vial is for single use only.

Reconstitution and dilution should be performed using aseptic techniques to ensure the sterility of the prepared suspension. The solvent vial should be warmed to room temperature and the powder vial should be tapped and shaken to ensure the powder is moving freely. After removal of the protective caps from the top of both vials the rubber stoppers should be cleaned with an alcohol swab. A 1 mL graduated syringe with 19 Gauge or wider needle should be used for withdrawing the solvent from its vial. The syringe should be filled with a volume of air equal to the required volume of the solvent for injection and the air injected into the solvent vial to make it easier to withdraw the solvent. The vial should be turned upside down, with the syringe in and the tip of the needle should be placed in the solvent. To remove any bubbles, the syringe should be tapped gently. The plunger should be pushed up gently, until all bubbles are removed from the syringe and needle. The syringe should be filled with the correct volume of the solvent for injection as listed above and the syringe needle withdrawn from the vial subsequently. Any remaining solvent should not be used for a second preparation.

Holding the needle against the inside vial wall, the entire contents of the syringe should be injected into the powder vial. Without touching the rubber top the vial should be swirled vigorously until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. The swirling should only be stopped once the suspension appears uniform, white and all the powder on the bottom is dispersed. After reconstitution the medicinal product should be used immediately before the suspension settles. If not used immediately, the suspension must be reconstituted again by swirling immediately before injection. The appropriate volume should be withdrawn in a sterile syringe via a sterile 26-gauge needle: The vial should be turned upside down, with the syringe in, and the tip of the needle should be placed in the suspension which is then slowly withdrawn. To remove small air bubbles the syringe should be tapped gently. The powder should be homogenously suspended in the injection vehicle prior to administration. The syringe should be held upright and gentle pressure applied to the plunger until a small drop of suspension appears at the end of the needle. The injection site should be cleaned with an alcohol swab and the suspension injected over a period of 5 seconds.

Detailed information on how to administer this medicinal product is provided in section 3 of the patient leaflet.

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)

EU/1/13/849/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 10 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial delivers 10 mg of somatropin* (corresponding to 30 IU)

After reconstitution, 0.5 mL of suspension contains 10 mg somatropin (20 mg/mL).

*produced in Saccharomyces cerevisiae by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

White or almost white powder. The solvent is a clear, oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatropin Biopartners is indicated in children and adolescents aged 2 to 18 years for long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone.

4.2 Posology and method of administration

Diagnosis and therapy with this medicinal product should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with growth hormone deficiency (GHD).

Posology

The recommended and maximum dose is 0.5 mg/kg/week and should not be exceeded. In children, Somatropin Biopartners should be administered subcutaneously at a concentration of 20 mg/mL. For dosage instruction, see table below.

It is recommended that a maximum injection volume of 1 mL per injection site, corresponding to a dose of 20 mg of somatropin, should not be exceeded.

For children heavier than 20 kg, Somatropin Biopartners 20 mg powder and solvent for prolonged-release suspension for injection is available.
For children heavier than 40 kg, two vials (a 10 mg and a 20 mg vial or two vials of 20 mg) can be used according to the body weight as indicated in the table below. The maximum injection volume per injection site should not exceed 1 mL. Therefore, in children weighing more than 40 kg the overall

injection volume must be divided into equal parts between two injection sites, as more than 1 mL of suspension is required.

Conversion from patient body weight to dose, number of vials, total injection volume and number of injections in paediatric patients

Patient bodyweight (kg)	Dose (mg)	Vials and solvent required for preparation of one dose*	Injection volume (mL)	Number of injections per dose
4	2	One 10-mg vial reconstituted with 0.7 mL solvent	0.1	1
6	3		0.15	
8	4		0.2	
10	5		0.25	
12	6		0.3	
14	7		0.35	
16	8		0.4	
18	9		0.45	
20	10		0.5	
22	11	One 20-mg vial reconstituted with 1.2 mL solvent	0.55	
24	12		0.6	
26	13		0.65	
28	14		0.7	
30	15		0.75	
32	16		0.8	
34	17		0.85	
36	18		0.9	
38	19		0.95	
40	20		1.0	
42	21	One 10-mg vial reconstituted with 0.7 mL solvent and One 20-mg vial reconstituted with 1.2 mL solvent	1.05	2
44	22		1.1	
46	23		1.15	
48	24		1.2	
50	25		1.25	
52	26		1.3	
54	27		1.35	
56	28		1.4	
58	29		1.45	
60	30		1.5	
62	31	Two 20-mg vials reconstituted with 1.2 mL solvent each	1.55	
64	32		1.6	
66	33		1.65	
68	34		1.7	
70	35		1.75	
72	36		1.8	
74	37		1.85	
76	38		1.9	
78	39		1.95	
80	40		2.0	

* Each vial contains an overfill of somatropin powder to allow the withdrawal of the required amount of somatropin when reconstituted. (see section 6.6).

Treatment with this medicinal product should be continued until final height has been reached or until epiphyseal closure.

Where childhood-onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass). For monitoring, the attainment of a normal peak bone mass defined as a T score > - 1 (i.e. standardised to average adult peak bone mass measured by dual energy X-ray absorptiometry taking into account gender and ethnicity) is one of the therapeutic objectives during the transition period. Once a normal peak bone mass is attained patients should be switched to Somatropin Biopartners for adults, if clinically indicated, and the dosing recommendation for adults should be followed.

Special populations

Renal/hepatic impairment
No information in patients with renal or hepatic impairment is available and particular dose recommendations cannot be given.

Paediatric population (below 2 years of age)
Somatropin Biopartners should not be used in infants below the age of 2 years.

Method of administration

The patient or carer should receive training to ensure understanding of the administration procedure before being allowed to (self-) inject.

Somatropin Biopartners is administered subcutaneously once a week. After reconstitution the injection should be administered immediately.

The subcutaneous injection should always be administered at the same time of the day to increase compliance and the site of injection must be varied to prevent lipoatrophy.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Somatropin must not be used when there is any evidence of tumour activity. Intracranial tumours must be inactive and antitumour therapy must be completed prior to the initiation of growth hormone therapy. Treatment should be discontinued if there is evidence of tumour (re)growth.
- Somatropin must not be used for growth promotion in children with closed epiphyses.
- Somatropin treatment must not be started in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure or similar conditions.

4.4 Special warnings and precautions for use

Malignancies

Patients with prior malignancies should be examined routinely for progression or recurrence.

In paediatric patients there is no evidence 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.

There is an increased risk that paediatric patients with prior malignancies may develop second neoplasm when treated with growth hormone, especially if treatment of the primary malignancy involved radiotherapy. These patients should be counselled on risks before initiating therapy.

Benign intracranial hypertension

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.

Insulin sensitivity

Because human growth hormone (hGH) may induce a state of insulin resistance and hyperglycaemia, patients treated with this medicinal product should be monitored for evidence of glucose intolerance. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin treatment is initiated. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Hypothyroidism may develop in patients with central subclinical hypothyroidism after initiating therapy with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to somatropin.
In patients with hypopituitarism receiving thyroxin replacement therapy, hyperpituitarism may develop. Thyroid function should therefore be closely monitored in all patients.

Adrenal function

Treatment with growth hormone may facilitate the development of adrenal insufficiency and potentially fatal adrenal crises in patients with organic GHD or idiopathic panhypopituitarism. It is therefore crucial to assess baseline and stress doses of glucocorticoids which may need to be adjusted when growth hormone therapy is initiated.

Other precautions

This medicinal product is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy 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.

After accidental intramuscular injection, hypoglycaemia may occur.

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

The recommended weekly dose in children (i.e. 0.5 mg/kg/week) should not be exceeded as there is limited experience with higher doses in this patient group.

Leukaemia

Leukaemia has been reported in a small number of GHD patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Scoliosis

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis.

Antibodies

Some patients may develop antibodies to this medicinal product. Somatropin Biopartners has given rise to the formation of antibodies in approximately 33% of the paediatric patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation. Testing for antibodies to somatropin may be considered in patients with otherwise unexplained lack of growth response.

Injection site reactions

Injection site related reactions, mostly swelling at the injection site, were reported in approximately 43% of the paediatric patients. Few patients discontinued treatment due to injections site reactions, see section 4.8.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy will inhibit the growth-promoting effect of hGH. Patients receiving concomitant glucocorticoid therapy should have their dose carefully adjusted to avoid an inhibitory effect on growth.

Growth hormone increases the extrathyroidal conversion of thyroxin (T4) to triiodothyronine (T3) and may unmask central hypothyroidism. Thyroxine replacement therapy may therefore need to be initiated or adjusted.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. Because hGH may induce a state of insulin resistance, an adjustment of the insulin dose may be required.

Somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Somatropin Biopartners is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of this medicinal product in pregnant women. Very limited data on exposure to other somatropin preparations during early pregnancy did not indicate an adverse pregnancy outcome. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
During normal pregnancy, levels of pituitary growth hormone fall markedly after 20 weeks of gestation, 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. Somatropin Biopartners is not recommended during pregnancy.

Breast-feeding

No clinical studies have been conducted with Somatropin Biopartners in breast-feeding women. It is unknown whether somatropin or its metabolites are excreted in human breast milk; however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Caution should be exercised when this medicinal product is administered to breast-feeding women.

Fertility

Animal studies with other somatropin formulations have shown adverse effects but the available nonclinical data are considered insufficient to draw firm conclusions on the use in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Somatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials included approximately 530 patients treated with Somatropin Biopartners. When adverse reactions occurred, they tended to be transient and severity was generally mild to moderate. The safety profile of Somatropin Biopartners is generally consistent with the well known safety profile of daily growth hormone treatments. The adverse reactions most commonly reported were injection site related reactions, peripheral oedema, headache, myalgia, arthralgia, paraesthesia, hypothyroidism and decreased free thyroxine.

Tabulated list of adverse reactions

The following adverse reactions have been observed under treatment with Somatropin Biopartners in a 12-month controlled comparative clinical study in 178 treatment naïve children with growth failure due to insufficient secretion of endogenous growth hormone and in a dose finding study. Additional reports based on published information for daily growth hormone treatments are listed with asterisks. The frequency of adverse reactions listed below is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data):

Immune system disorders
Very common: Formation of antibodies against growth hormone (33%), see section “Descriptions of selected adverse reactions”, under “Immunogenicity”.

Endocrine disorders
Common: Hypercortisolism (7.7%)**,** hypothyroidism (2.2%), adrenal cortical insufficiency (3.3%), hypothyreosis secondary to TSH deficiency (2.6%), decreased free thyroxine (4.4%), increased blood TSH (2.2%)

Metabolism and nutrition disorders
Common: Mild hyperglycaemia*
Not known: Insulin resistance*

Psychiatric disorders
Very rare: insomnia*

Nervous system disorders
Common: headache (4.4%), lethargy (1.1%), dizziness (2.6%)
Rare: paraesthesia*

Vascular disorders
Rare: hypertension*

Gastrointestinal disorders
Common: vomitting (1.1%), abdominal pain (1.1%)

Skin and subcutaneous tissue disorders
Common: pigmentation disorder (1.1%)

Musculoskeletal and connective tissue disorders
Common: arthralgia (1.1%), pain in extremities (5.1%)

Reproductive system and breast disorders
Very rare: gynaecomastia*

General disorders and administration site conditions
Very common: injection site swelling (30.8%)
Common: injection site pain (9.9%), injection site discolouration (8.8%), injection site erythema (7.7%), injection site nodule (4.4%), injection site reaction (1.1%), injection site warmth (1.1%), pyrexia (2.6%), oedema (local and generalised)*

Investigations
Common: decreased blood cortisol (2.2%)

Description of selected adverse reactions

Injection site reactions
The most frequently reported adverse reactions in children were injection site related reactions, most of them being mild to moderate in intensity. Few patients discontinued treatment due to injections site reactions.

Immunogenicity
In the pivotal paediatric study, antibody responses to somatropin at two or more consecutive visits were observed in 33% of the patients. No effect on safety or efficacy was observed. It is unlikely that the antibody responses to treatment with Somatropin Biopartners are of clinical relevance.

With regard to antibodies against host cell proteins, low anti-S. cerevisiae protein antibody titres similar to levels in the normal untreated population were found in some patients treated with this medicinal product. The generation of such antibodies with low binding activity is unlikely to be clinically relevant.

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Due to the prolonged-release characteristics of this medicinal product peak levels of growth hormone can be expected approximately 15 hours after injection, see section 5.2. Long term over-dosing could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of hGH excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and agonists, ATC code: H01AC01

The somatropin in this medicinal product 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 active substance is identical to that of hGH of pituitary origin. The somatropin in this medicinal product is synthesised in yeast (*Saccharomyces cerevisiae*).

Mechanism of action

The biological effects of somatropin are equivalent to those of hGH of pituitary origin.

The most prominent effect of somatropin in children is the stimulation of the growth plates of long bones. Additionally, it promotes cellular protein synthesis and nitrogen retention.

Pharmacodynamic effects

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in patients with -GHD, 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.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical efficacy and safety

In a randomized, parallel-group, multicentre Phase III study, 178 children between 3 and 12 years of age with organic and/or idiopathic GHD were randomised to receive either weekly administered Somatropin Biopartners (0.5 mg/kg/week) or daily administered recombinant hGH (0.03 mg/kg/day) for 12 months. The results showed weekly administered Somatropin Biopartners to be non inferior to daily administered recombinant hGH with respect to the primary endpoint of height velocity after 12 months. Similar results were achieved for all other parameters assessed including height SDS (standard deviation score), bone maturation, IGF-I and IGF BP-3. In the children receiving Somatropin Biopartners a higher incidence of (non-serious) injection site reactions and a higher rate of formation of (non-neutralising) antibodies against somatropin as compared to children with daily administered recombinant growth hormone were observed (see also sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 0.5 mg/kg prolonged release somatropin to prepubertal children with GHD the C_{max} and t_{max} of plasma hGH were about 60.7 ng/mL and 12.0 h respectively. In general, C_{max} and AUC increased approximately proportionally with dose over a dose range of 0.2 to 0.7 mg/kg in prepubertal children with GHD. The apparent terminal half-life was about 7.4 h in children, presumably reflecting slow absorption from the site of injection.
The t_{max} was later and the half-life longer following the administration of Somatropin Biopartners than when immediate release products had been previously administered once daily to the same subjects reflecting the slower and more prolonged release of hGH from the site of injection of Somatropin Biopartners.

Distribution

No accumulation of hGH following multiple dosing of this medicinal product has been observed.

Biotransformation / Elimination

The metabolic fate of hGH involves classical protein catabolism in both the liver and kidney.

5.3 Preclinical safety data

Non-clinical pharmacokinetic and pharmacodynamic studies in dogs and juvenile monkeys showed that Somatropin Biopartners released recombinant hGH in a prolonged manner and increased serum IGF-I for an extended period up to 5-6 days.

Non-clinical data revealed no specific hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

Long term carcinogenicity studies with Somatropin Biopartners have not been conducted. There are no specific studies which address local tolerance in animals after subcutaneous injection, but data available from the repeated-dose toxicity studies revealed swelling and inflammatory infiltrate at the injection sites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium hyaluronate
Egg phospholipids
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous.

Solvent:
Medium chain triglycerides.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After reconstitution: From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Powder: Vial (type I glass) closed with a rubber stopper (butyl) and a light-green flip-off cap (aluminium and plastic).
Solvent: Vial (Type I glass) closed with a rubber stopper (butyl) and a flip-off cap (aluminium and plastic).

Each vial of powder delivers 10 mg somatropin; each vial of solvent contains 1.5 mL liquid.

Pack sizes:
1 vial of powder and 1 vial of solvent.
4 vials of powder and 4 vials of solvent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

Somatropin Biopartners 10 mg should be reconstituted with 0.7 mL solvent.

The suspension should appear uniform and white.

The 10-mg vial contains an overfill of somatropin powder to allow the withdrawal of up to 10 mg (0.5 mL suspension) of somatropin when reconstituted.

Each vial is for single use only.

Reconstitution and dilution should be performed using aseptic techniques to ensure the sterility of the prepared suspension. The solvent vial should be warmed to room temperature and the powder vial should be tapped and shaken to ensure the powder is moving freely. After removal of the protective caps from the top of both vials the rubber stoppers should be cleaned with an alcohol swab. A 1 mL graduated syringe with 19 Gauge or wider needle should be used for withdrawing the solvent from its vial. The syringe should be filled with a volume of air equal to the required volume of the solvent for injection and the air injected into the solvent vial to make it easier to withdraw the solvent. The vial should be turned upside down, with the syringe in and the tip of the needle should be placed in the solvent. To remove any bubbles, the syringe should be tapped gently. The plunger should be pushed up gently, until all bubbles are removed from the syringe and needle. The syringe should be filled with the correct volume of the solvent for injection as listed above and the syringe needle withdrawn from the vial subsequently. Any remaining solvent should not be used for a second preparation.

Holding the needle against the inside vial wall, the entire contents of the syringe should be injected into the powder vial. Without touching the rubber top the vial should be swirled vigorously until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. The swirling should only be stopped once the suspension appears uniform, white and all the powder on the bottom is dispersed. After reconstitution the medicinal product should be used immediately before the suspension settles. If not used immediately, the suspension must be reconstituted again by swirling immediately before injection. The appropriate volume should be withdrawn in a sterile syringe via a sterile 26-gauge needle: The vial should be turned upside down, with the syringe in, and the tip of the needle should be placed in the suspension which is then slowly withdrawn. To remove small air bubbles the syringe should be tapped gently. The powder should be homogenously suspended in the injection vehicle prior to administration.
The syringe should be held upright and gentle pressure applied to the plunger until a small drop of suspension appears at the end of the needle. The injection site should be cleaned with an alcohol swab and the suspension injected over a period of 5 seconds.

Detailed information on how to administer this medicinal product is provided in section 3 of the patient leaflet.

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)

EU/1/13/849/004
EU/1/13/849/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 20 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial delivers 20 mg of somatropin* (corresponding to 60 IU)

After reconstitution, 1 mL of suspension contains 20 mg somatropin (20 mg/mL).

*produced in Saccharomyces cerevisiae by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

White or almost white powder. The solvent is a clear, oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatropin Biopartners is indicated in children and adolescents aged 2 to 18 years for long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone.

4.2 Posology and method of administration

Diagnosis and therapy with this medicinal product should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with growth hormone deficiency (GHD).

Posology

The recommended and maximum dose is 0.5 mg/kg / week and should not be exceeded. In children, Somatropin Biopartners should be administered subcutaneously at a concentration of 20 mg/mL. For dosage instruction, see table below.
It is recommended that a maximum injection volume of 1 mL per injection site, corresponding to a dose of 20 mg of somatropin, should not be exceeded.

For children up to 20 kg Somatropin Biopartners 10 mg powder and solvent for prolonged-release suspension for injection is available.
The maximum retrievable amount of somatropin in one vial of suspension is 20 mg which is sufficient for administration in children of up to 40 kg bodyweight. For children heavier than 40 kg, two vials (a 10 mg and a 20 mg vial or two vials of 20 mg) can be used according to the body weight as indicated in the table below. The maximum injection volume per injection site should not exceed 1 mL.

Therefore, in children weighing more than 40 kg the overall injection volume must be divided into equal parts between two injection sites, as more than 1 mL of suspension is required.

Conversion from patient body weight to dose, number of vials, total injection volume and number of injections in paediatric patients

Patient bodyweight (kg)	Dose (mg)	Vials and solvent required for preparation of one dose*	Injection volume (mL)	Number of injections per dose
4	2	One 10-mg vial reconstituted with 0.7 mL solvent	0.1	1
6	3		0.15	
8	4		0.2	
10	5		0.25	
12	6		0.3	
14	7		0.35	
16	8		0.4	
18	9		0.45	
20	10		0.5	
22	11	One 20-mg vial reconstituted with 1.2 mL solvent	0.55	
24	12		0.6	
26	13		0.65	
28	14		0.7	
30	15		0.75	
32	16		0.8	
34	17		0.85	
36	18		0.9	
38	19		0.95	
40	20		1.0	
42	21	One 10-mg vial reconstituted with 0.7 mL solvent and One 20-mg vial reconstituted with 1.2 mL solvent	1.05	2
44	22		1.1	
46	23		1.15	
48	24		1.2	
50	25		1.25	
52	26		1.3	
54	27		1.35	
56	28		1.4	
58	29		1.45	
60	30		1.5	
62	31	Two 20-mg vials reconstituted with 1.2 mL solvent each	1.55	
64	32		1.6	
66	33		1.65	
68	34		1.7	
70	35		1.75	
72	36		1.8	
74	37		1.85	
76	38		1.9	
78	39		1.95	
80	40		2.0	

* Each vial contains an overfill of somatropin powder to allow the withdrawal of the required amount of somatropin when reconstituted. (see section 6.6).

Treatment with this medicinal product should be continued until final height has been reached or until epiphyseal closure.

Where childhood-onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass). For monitoring, the attainment of a normal peak bone mass defined as a T score > - 1 (i.e. standardised to average adult peak bone mass measured by dual energy X-ray absorptiometry taking into account gender and ethnicity) is one of the therapeutic objectives during the transition period. Once a normal peak bone mass is attained patients should be switched to Somatropin Biopartners for adults, if clinically indicated, and the dosing recommendation for adults should be followed.

Special populations

Renal/hepatic impairment
No information in patients with renal or hepatic impairment is available and particular dose recommendations cannot be given.

Paediatric population (below 2 years of age)
Somatropin Biopartners should not be used in infants below the age of 2 years.

Method of administration

The patient or carer should receive training to ensure understanding of the administration procedure before being allowed to (self-) inject.

Somatropin Biopartners is administered subcutaneously once a week. After reconstitution the injection should be administered immediately.

The subcutaneous injection should always be administered at the same time of the day to increase compliance and the site of injection must be varied to prevent lipoatrophy.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Somatropin must not be used when there is any evidence of tumour activity. Intracranial tumours must be inactive and antitumour therapy must be completed prior to the initiation of growth hormone therapy. Treatment should be discontinued if there is evidence of tumour (re)growth.
- Somatropin must not be used for growth promotion in children with closed epiphyses.
- Somatropin treatment must not be started in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure or similar conditions.

4.4 Special warnings and precautions for use

Malignancies

Patients with prior malignancies should be examined routinely for progression or recurrence.

In paediatric patients there is no evidence 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.

There is an increased risk that paediatric patients with prior malignancies may develop second neoplasm when treated with growth hormone, especially if treatment of the primary malignancy involved radiotherapy. These patients should be counselled on risks before initiating therapy.

Benign intracranial hypertension

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.

Insulin sensitivity

Because human growth hormone (hGH) may induce a state of insulin resistance and hyperglycaemia, patients treated with this medicinal product should be monitored for evidence of glucose intolerance. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin treatment is initiated. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Hypothyroidism may develop in patients with central subclinical hypothyroidism after initiating therapy with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to somatropin.
In patients with hypopituitarism receiving thyroxin replacement therapy, hyperpituitarism may develop. Thyroid function should therefore be closely monitored in all patients.

Adrenal function

Treatment with growth hormone may facilitate the development of adrenal insufficiency and potentially fatal adrenal crises in patients with organic GHD or idiopathic panhypopituitarism. It is therefore crucial to assess baseline and stress doses of glucocorticoids which may need to be adjusted when growth hormone therapy is initiated.

Other precautions

This medicinal product is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy 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.

After accidental intramuscular injection, hypoglycaemia may occur.

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

The recommended weekly dose in children (i.e. 0.5 mg/kg/week) should not be exceeded as there is limited experience with higher doses in this patient group.

Leukaemia

Leukaemia has been reported in a small number of GHD patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Scoliosis

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis.

Antibodies

Some patients may develop antibodies to this medicinal product. Somatropin Biopartners has given rise to the formation of antibodies in approximately 33% of the paediatric patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation. Testing for antibodies to somatropin may be considered in patients with otherwise unexplained lack of growth response.

Injection site reactions

Injection site related reactions, mostly swelling at the injection site, were reported in approximately 43% of the paediatric patients. Few patients discontinued treatment due to injections site reactions, see section 4.8.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy will inhibit the growth-promoting effect of hGH. Patients receiving concomitant glucocorticoid therapy should have their dose carefully adjusted to avoid an inhibitory effect on growth.

Growth hormone increases the extrathyroidal conversion of thyroxin (T4) to triiodothyronine (T3) and may unmask central hypothyroidism. Thyroxine replacement therapy may therefore need to be initiated or adjusted.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. Because hGH may induce a state of insulin resistance, an adjustment of the insulin dose may be required.

Somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Somatropin Biopartners is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of this medicinal product in pregnant women. Very limited data on exposure to other somatropin preparations during early pregnancy did not indicate an adverse pregnancy outcome. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
During normal pregnancy, levels of pituitary growth hormone fall markedly after 20 weeks of gestation, 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. Somatropin Biopartners is not recommended during pregnancy.

Breast-feeding

No clinical studies have been conducted with Somatropin Biopartners in breast-feeding women. It is unknown whether somatropin or its metabolites are excreted in human breast milk; however, absorption of intact protein from the gastrointestinal tract of the infant is unlikely. Caution should be exercised when this medicinal product is administered to breast-feeding women.

Fertility

Animal studies with other somatropin formulations have shown adverse effects but the available nonclinical data are considered insufficient to draw firm conclusions on the use in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Somatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical trials included approximately 530 patients treated with Somatropin Biopartners. When adverse reactions occurred, they tended to be transient and severity was generally mild to moderate. The safety profile of Somatropin Biopartners is generally consistent with the well known safety profile of daily growth hormone treatments. The adverse reactions most commonly reported were injection site related reactions, peripheral oedema, headache, myalgia, arthralgia, paraesthesia, hypothyroidism and decreased free thyroxine.

Tabulated list of adverse reactions

The following adverse reactions have been observed under treatment with Somatropin Biopartners in a 12-month controlled comparative clinical study in 178 treatment naïve children with growth failure due to insufficient secretion of endogenous growth hormone and in a dose finding study. Additional reports based on published information for daily growth hormone treatments are listed with asterisks. The frequency of adverse reactions listed below is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data):

Immune system disorders
Very common: Formation of antibodies against growth hormone (33%), see section “Descriptions of selected adverse reactions”, under “Immunogenicity”

Endocrine disorders
Common: Hypercortisolism (7.7%)**,** hypothyroidism (2.2%), adrenal cortical insufficiency (3.3%), hypothyreosis secondary to TSH deficiency (2.6%), decreased free thyroxine (4.4%), increased blood TSH (2.2%)

Metabolism and nutrition disorders
Common: Mild hyperglycaemia*
Not known: Insulin resistance*

Psychiatric disorders
Very rare: insomnia*

Nervous system disorders
Common: headache (4.4%), lethargy (1.1%), dizziness (2.6%)
Rare: paraesthesia*

Vascular disorders
Rare: hypertension*

Gastrointestinal disorders
Common: vomitting (1.1%), abdominal pain (1.1%)

Skin and subcutaneous tissue disorders
Common: pigmentation disorder (1.1%)

Musculoskeletal and connective tissue disorders
Common: arthralgia (1.1%), pain in extremities (5.1%)

Reproductive system and breast disorders
Very rare: gynaecomastia*

General disorders and administration site conditions
Very common: injection site swelling (30.8%)
Common: injection site pain (9.9%), injection site discolouration (8.8%), injection site erythema (7.7%), injection site nodule (4.4%), injection site reaction (1.1%), injection site warmth (1.1%), pyrexia (2.6%), oedema (local and generalised)*

Investigations
Common: decreased blood cortisol (2.2%)

Description of selected adverse reactions

Injection site reactions
The most frequently reported adverse reactions in children were injection site related reactions, most of them being mild to moderate in intensity. Few patients discontinued treatment due to injections site reactions.

Immunogenicity
In the pivotal paediatric study, antibody responses to somatropin at two or more consecutive visits were observed in 33% of the patients. No effect on safety or efficacy was observed. It is unlikely that the antibody responses to treatment with Somatropin Biopartners are of clinical relevance.

With regard to antibodies against host cell proteins, low anti-S. cerevisiae protein antibody titres similar to levels in the normal untreated population were found in some patients treated with this medicinal product. The generation of such antibodies with low binding activity is unlikely to be clinically relevant.

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Due to the prolonged-release characteristics of this medicinal product peak levels of growth hormone can be expected approximately 15 hours after injection, see section 5.2. Long term over-dosing could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of hGH excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and agonists, ATC code: H01AC01

The somatropin in this medicinal product 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 active substance is identical to that of hGH of pituitary origin. The somatropin in this medicinal product is synthesised in yeast (*Saccharomyces cerevisiae*).

Mechanism of action

The biological effects of somatropin are equivalent to those of hGH of pituitary origin.

The most prominent effect of somatropin in children is the stimulation of the growth plates of long bones. Additionally, it promotes cellular protein synthesis and nitrogen retention.

Pharmacodynamic effects

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in patients with -GHD, 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.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical efficacy and safety

In a randomized, parallel-group, multicentre Phase III study, 178 children between 3 and 12 years of age with organic and/or idiopathic GHD were randomised to receive either weekly administered Somatropin Biopartners (0.5 mg/kg/week) or daily administered recombinant hGH (0.03 mg/kg/day) for 12 months. The results showed weekly administered Somatropin Biopartners to be non inferior to daily administered recombinant hGH with respect to the primary endpoint of height velocity after 12 months. Similar results were achieved for all other parameters assessed including height SDS

(standard deviation score), bone maturation, IGF-I and IGF BP-3. In the children receiving Somatropin Biopartners a higher incidence of (non-serious) injection site reactions and a higher rate of formation of (non-neutralising) antibodies against somatropin as compared to children with daily administered recombinant growth hormone were observed (see also sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 0.5 mg/kg prolonged release somatropin to prepubertal children with GHD the C_{max} and t_{max} of plasma hGH were about 60.7 ng/mL and 12.0 h respectively. In general, C_{max} and AUC increased approximately proportionally with dose over a dose range of 0.2 to 0.7 mg/kg in prepubertal children with GHD. The apparent terminal half-life was about 7.4 h in children, presumably reflecting slow absorption from the site of injection.
The t_{max} was later and the half-life longer following the administration of Somatropin Biopartners than when immediate release products had been previously administered once daily to the same subjects reflecting the slower and more prolonged release of hGH from the site of injection of Somatropin Biopartners.

Distribution

No accumulation of hGH following multiple dosing of this medicinal product has been observed.

Biotransformation / Elimination

The metabolic fate of hGH involves classical protein catabolism in both the liver and kidney.

5.3 Preclinical safety data

Non-clinical pharmacokinetic and pharmacodynamic studies in dogs and juvenile monkeys showed that Somatropin Biopartners released recombinant hGH in a prolonged manner and increased serum IGF-I for an extended period up to 5-6 days.

Non-clinical data revealed no specific hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

Long term carcinogenicity studies with Somatropin Biopartners have not been conducted. There are no specific studies which address local tolerance in animals after subcutaneous injection, but data available from the repeated-dose toxicity studies revealed swelling and inflammatory infiltrate at the injection sites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium hyaluronate
Egg phospholipids
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous.

Solvent:
Medium chain triglycerides.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After reconstitution: From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Powder: Vial (type I glass) closed with a rubber stopper (butyl) and a green flip-off cap (aluminium and plastic).
Solvent: Vial (Type I glass) closed with a rubber stopper (butyl) and a flip-off cap (aluminium and plastic).

Each vial of powder delivers 20 mg somatropin; each vial of solvent contains 1.5 mL liquid.

Pack sizes:
1 vial of powder and 1 vial of solvent.
4 vials of powder and 4 vials of solvent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

Somatropin Biopartners 20 mg should be reconstituted with 1.2 mL solvent.

The suspension should appear uniform and white.

The 20-mg vial contains an overfill of somatropin powder to allow the withdrawal of up to 20 mg (1 mL suspension) of somatropin when reconstituted.

Each vial is for single use only.

Reconstitution and dilution should be performed using aseptic techniques to ensure the sterility of the prepared suspension. The solvent vial should be warmed to room temperature and the powder vial should be tapped and shaken to ensure the powder is moving freely. After removal of the protective caps from the top of both vials the rubber stoppers should be cleaned with an alcohol swab. A 1 mL graduated syringe with 19 Gauge or wider needle should be used for withdrawing the solvent from its vial. The syringe should be filled with a volume of air equal to the required volume of the solvent for injection and the air injected into the solvent vial to make it easier to withdraw the solvent. The vial should be turned upside down, with the syringe in and the tip of the needle should be placed in the solvent. To remove any bubbles, the syringe should be tapped gently. The plunger should be pushed up gently, until all bubbles are removed from the syringe and needle. The syringe should be filled with the correct volume of the solvent for injection as listed above and the syringe needle withdrawn from the vial subsequently. Any remaining solvent should not be used for a second preparation.

Holding the needle against the inside vial wall, the entire contents of the syringe should be injected into the powder vial. Without touching the rubber top the vial should be swirled vigorously until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. The swirling should only be stopped once the suspension appears uniform, white and all the powder on the bottom is dispersed. After reconstitution the medicinal product should be used immediately before the suspension settles. If not used immediately, the suspension must be reconstituted again by swirling immediately before injection. The appropriate volume should be withdrawn in a sterile syringe via a sterile 26-gauge needle: The vial should be turned upside down, with the syringe in, and the tip of the needle should be placed in the suspension which is then slowly withdrawn. To remove small air bubbles the syringe should be tapped gently. The powder should be homogenously suspended in the injection vehicle prior to administration.
The syringe should be held upright and gentle pressure applied to the plunger until a small drop of suspension appears at the end of the needle. The injection site should be cleaned with an alcohol swab and the suspension injected over a period of 5 seconds.

Detailed information on how to administer this medicinal product is provided in section 3 of the patient leaflet.

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)

EU/1/13/849/006
EU/1/13/849/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

LG Life Sciences, Ltd.
129, Seokam-ro
Iksan-si, Jeollabuk-do
South Korea

Name and address of the manufacturer(s) responsible for batch release

BIOTON S.A.
Macierzysz, 12, Poznanska, Str.,
05-850 Ozarow Mazowiecki,
Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON SOMATROPIN BIOPARTNERS 2 MG

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 2 mg powder and solvent for prolonged-release suspension for injection somatropin
For adults

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One powder vial delivers 2 mg of somatropin (6 IU). After reconstitution, 0.2 mL of suspension contains 2 mg (10 mg/mL).

3. LIST OF EXCIPIENTS

Powder: sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous.
Solvent: medium chain triglycerides.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

4 vials of 2 mg powder
4 vials of 1.5 mL solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once weekly
Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After reconstitution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/001 4 vials of powder and 4 vials of solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Somatropin Biopartners 2 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 2 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Somatropin Biopartners 2 mg powder for prolonged-release suspension for injection
somatropin
SC
For adults

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg (6 IU)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON SOMATROPIN BIOPARTNERS 4 MG

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 4 mg powder and solvent prolonged-release for suspension for injection somatropin
For adults

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One powder vial delivers 4 mg of somatropin (12 IU). After reconstitution, 0.4 mL of suspension contains 4 mg (10 mg/mL).

3. LIST OF EXCIPIENTS

Powder: sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous.
Solvent: medium chain triglycerides.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection
4 vials of 4 mg powder
4 vials of 1.5 mL solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After reconstitution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/002 4 vials of powder and 4 vials of solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Somatropin Biopartners 4 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 4 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Somatropin Biopartners 4 mg powder for prolonged-release suspension for injection
somatropin
SC
For adults

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg (12 IU)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON SOMATROPIN BIOPARTNERS 7 MG

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 7 mg powder and solvent for prolonged-release suspension for injection
Somatropin
For adults

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One powder vial delivers 7 mg of somatropin (21 IU). After reconstitution, 0.7 mL of suspension contains 7 mg (10 mg/mL).

3. LIST OF EXCIPIENTS

Powder: sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous.
Solvent: medium chain triglycerides.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection
4 vials of 7 mg powder
4 vials of 1.5 mL solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After reconstitution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/003 4 vials of powder and 4 vials of solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Somatropin Biopartners 7 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 7 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Somatropin Biopartners 7 mg powder for prolonged-release suspension for injection
somatropin
SC
For adults

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7 mg (21 IU)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT SOMATROPIN BIOPARTNERS 10 MG

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 10 mg powder and solvent for prolonged-release suspension for injection somatropin
For children and adolescents (2 to 18 years)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One powder vial delivers 10 mg of somatropin (30 IU). After reconstitution, 0.5 mL of suspension contains 10 mg (20 mg/mL).

3. LIST OF EXCIPIENTS

Powder: sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous.
Solvent: medium chain triglycerides.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection
1 vial of 10 mg powder
1 vial of 1.5 mL solvent
4 vials of 10 mg powder
4 vials of 1.5 mL solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After reconstitution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/004 1 vial of powder and 1 vial of solvent
EU/1/13/849/005 4 vials of powder and 4 vials of solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Somatropin Biopartners 10 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 10 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Somatropin Biopartners 10 mg powder for prolonged-release suspension for injection.
somatropin
SC
For children and adolescents (2 to 18 years)

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg (30 IU)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT SOMATROPIN BIOPARTNERS 20 MG

1. NAME OF THE MEDICINAL PRODUCT

Somatropin Biopartners 20 mg powder and solvent for prolonged-release suspension for injection somatropin
For children and adolescents (2 to 18 years)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One powder vial delivers 20 mg of somatropin (60 IU). After reconstitution, 1 mL of suspension contains 20 mg (20 mg/mL).

3. LIST OF EXCIPIENTS

Powder: sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous.
Solvent: medium chain triglycerides.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection
20 mg powder in a vial and 1.5 mL solvent in a vial
1 vial of 20 mg powder
1 vial of 1.5 mL solvent
4 vials of 20 mg powder
4 vials of 1.5 mL solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After reconstitution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/849/006 1 vial of powder and 1 vial of solvent
EU/1/13/849/007 4 vials of powder and 4 vials of solvent

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Somatropin Biopartners 20 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 20 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Somatropin Biopartners 20 mg powder for prolonged-release suspension for injection
somatropin
SC
For children and adolescents (2 to 18 years)

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg (60 IU)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Somatropin Biopartners

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL medium chain triglycerides

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Somatropin Biopartners 2 mg powder and solvent for prolonged-release suspension for injection
Somatropin Biopartners 4 mg powder and solvent for prolonged-release suspension for injection
Somatropin Biopartners 7 mg powder and solvent for prolonged-release suspension for injection

For adults

Somatropin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Somatropin Biopartners is and what it is used for

Somatropin Biopartners contains human growth hormone, also called somatropin. Growth hormone regulates the growth and development of cells.

This medicine is used to treat adults with a lack (deficiency) of growth hormone who
- already had growth hormone deficiency when they were children or
- do not have enough growth hormone during adulthood.

2. What you need to know before you use Somatropin Biopartners

Do not use Somatropin Biopartners

- if you are allergic to somatropin or any of the other ingredients of this medicine (listed in section 6);
- if you have cancer;
  Tell your doctor if you have an active tumour (cancer). Tumours must be inactive and cancer therapy complete before you can start your treatment with growth hormone. Your doctor will stop your treatment with this medicine if there is evidence of cancerous growth;
- if you are ill due to a serious heart or stomach operation;

- if you are being treated for more than one injury following a serious accident;
- if you experience sudden serious breathing problems.

Warnings and precautions

Talk to your doctor before using Somatropin Biopartners if you:
- are an adult who has been treated with growth hormone during childhood:
  Your doctor will re-examine you for lack of growth hormone before restarting/continuing treatment;
- have a hereditary disease called Prader-Willi syndrome:
  You should not be treated with this medicine unless you also have a lack of growth hormone;
- have had a tumour:
  Your doctor will examine you frequently to ensure that the tumour has not come back;
- have symptoms like severe and recurrent headache, visual changes, nausea and/or vomiting which may be due to increased pressure in the skull during growth hormone treatment;
- suffer from an organic growth hormone deficiency (lack of growth hormone due to damage to the pituitary gland or the part of the brain called the hypothalamus) or decreased secretion of pituitary gland hormones:
  Your doctor will check your levels of adrenal hormones (glucocorticoids) which may require adjustment once growth hormone therapy begins.

Monitoring during treatment

- Your doctor may check the level of sugar in your urine or blood since it may be affected by this medicine.
- You must have regular thyroid function tests as this medicine can affect the amount of thyroid hormone in the blood.
  If the thyroid is not working properly, this medicine may not work as well as it should.

Children and adolescents

For the treatment of children and adolescents aged 2 to 18 years vials with 10 mg and 20 mg somatropin should be used.

Other medicines and Somatropin Biopartners

Tell your doctor or pharmacist if you are using, have recently used or are planning to use any other medicines.

In particular, inform your doctor if you are taking or have recently taken any of the following medicines. Your doctor may need to adjust the dose of Somatropin Biopartners or of the other medicines:
- corticosteroids, such as cortisone or prednisolone: medicines to reduce inflammation or immune system activity, to prevent organ transplant rejection or to treat asthma
- thyroxine: a medicine to treat reduced thyroid gland function
- insulin: a medicine to lower blood sugar levels
  The doctor will carefully monitor you during treatment as the effect of insulin may be reduced.
- oestrogen taken orally or other sex hormones
- medicines to treat epilepsy
- cyclosporine: a medicine to suppress the immune system

Pregnancy and breast-feeding

You should not use Somatropin Biopartners if you are pregnant or are trying to become pregnant.
If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if this medicine passes into breast milk. If you are breast-feeding only use this medicine if your doctor indicates it is clearly necessary.

Driving and using machines

Somatropin Biopartners has no or negligible effects on the ability to drive and use machines.

Important information about some of the ingredients of Somatropin Biopartners

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

3. How to use Somatropin Biopartners

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

This medicince is injected once a week.

The dose will be calculated by your doctor as described below. Individual doses may vary and your doctor will always prescribe the minimum effective dose based on your specific need.

Your dose should be checked every 6 months by your doctor.

The recommended starting dose is 2 mg of somatropin injected once a week. For women taking oral oestrogens the starting dose is usually 3 mg injected once a week.
Your doctor may decide upon a lower starting dose. If necessary, your doctor will gradually increase this dose according to your individual response to the treatment and your blood levels of a growth factor called IGF-I. The blood levels of IGF-I require regular monitoring so that they can be kept within the normal range for your age and gender.

Dosage reductions may be necessary:
- in patients above 60 years of age
- in patients who develop long lasting tissue swelling caused by fluid retention or who develop abnormal sensations such as prickling, tingling and itchiness
- to avoid the development of carpal tunnel syndrome, where the nerve running through the wrist (the median nerve) becomes squeezed, resulting in hand numbness and pain
- following use of the medicine over an extended period of time, particularly in men.

Please also see the required adjustments described in section 2, 'Other medicines and Somatropin Biopartners'.

Method of administration

After the powder is evenly mixed with the solvent provided, this medicine is injected under the skin. This means that after preparation, the suspension is injected with a short needle into the fatty skin tissue. After the injection, growth hormone is slowly released into your body over a period of about a week.

Injections should always be given on the same day of the week and at the same time of day because it is easier to remember.

If you are injecting this medicine yourself you will be shown how to prepare and give the injection. Do not inject this medicine yourself unless you have received training and you understand the procedure.

Inject the medicine as instructed by your doctor who will also tell you what dose to use and how to inject this dose with the vials you have been prescribed. Fatty tissue under the skin can shrink at the site of injection on repeated administration at the same site. To avoid this, always change the injection site between injections. This gives your skin and the area under your skin time to recover from one injection before it gets another one in the same place.

Accidental injection of this medicine into the muscle instead of under the skin may result in blood sugar levels becoming too low. Contact your doctor if this happens.

Information about self-injection of Somatropin Biopartners

Follow the instructions carefully step by step.

Collect the following items before you begin:
- supplied in the pack
  - Somatropin Biopartners vial containing active substance
  - Somatropin Biopartners vial containing 1.5 mL solvent for suspension for injection
- not supplied in the pack
  - one sterile injection syringe with 19 (19G) or wider Gauge needle to withdraw the solvent
  - one sterile injection syringe with 26 Gauge (26G) needle for the injection
  - alcohol swabs
  - dry gauze or cotton pad
  - an adhesive plaster
  - disposal box for used syringes and needles

Preparing the suspension

1. Remove the carton from the refrigerator. Wash your hands thoroughly with soap and water and dry them with a clean towel before preparing your injection. This helps to prevent infection.

2. Warm the solvent vial to room temperature by gently rolling it between your hands. Tap and shake the vial of powder to make sure the powder is moving freely.

3. Remove the protective caps from the top of both vials as seen in figure 3a. Clean the rubber stopper of both vials with an alcohol swab (figure 3b).

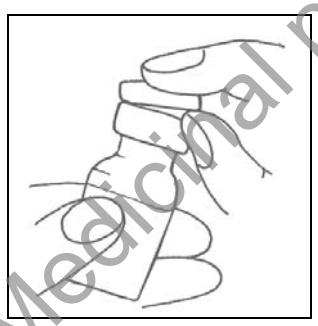

figure 3a

figure 3b

4. Use a 1 mL graduated syringe with a 19G or wider needle for withdrawing the solvent from its vial. Remove the needle guard and fill the syringe with a volume of air equal to the required volume of the solvent for injection, making it easier to withdraw the solvent:

- 0.4 mL in a 1 mL graduated syringe for Somatropin Biopartners 2 mg
- 0.6 mL in a 1 mL graduated syringe for Somatropin Biopartners 4 mg
- 0.9 mL in a 1 mL graduated syringe for Somatropin Biopartners 7 mg

Insert the needle through the centre of the rubber stopper of the solvent vial and inject all of the air into the vial.

figure 4

5. Turn the vial upside down, with the syringe inside and place the tip of the needle in the solvent as seen in figure 5. Slowly withdraw the required volume of solvent.
To remove any bubbles, gently tap the syringe. Apply gentle pressure by pushing the plunger up, until all bubbles are removed from the syringe and needle. Continue to fill the syringe with the correct volume of the solvent for injection, as described in the text of figure 4 above. Withdraw the syringe needle from the vial. Do not use any remaining solvent for a second preparation!

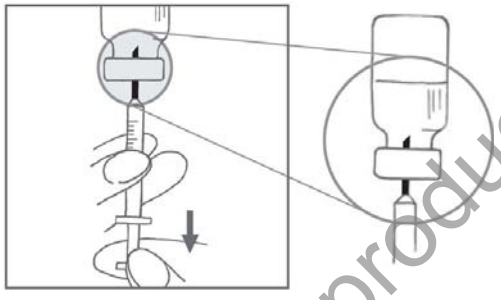

figure 5

6. Inject the entire contents of the syringe into the vial of powder, holding the syringe against the vial wall. Withdraw the syringe and discard it.

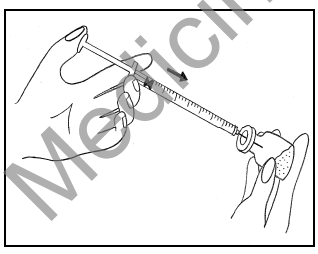

figure 6

7. Vigorously swirl the vial without touching the rubber top with your fingers until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. Only stop swirling the vial once the suspension appears uniform, white and all the powder on the bottom is dispersed. Use immediately, as the suspension may settle if left standing.
Do not use this medicine if you notice that it cannot be properly mixed.

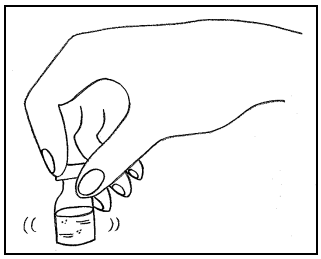

figure 7

Withdrawing the suspension

8. Clean the rubber stopper again with an unused alcohol swab.
Take a new syringe with a 26G needle. Remove the needle guard. Insert the needle straight through the centre of the vial's rubber stopper into the suspension.

figure 8

9. Turn the vial upside down, with the syringe in and place the tip of the needle in the suspension as shown in figure 9. Slowly withdraw the suspension. Because it is a thick mixture, the syringe might fill slowly. If the flow stops or bubbles appear, gently tap the syringe with your fingers. Apply gentle pressure to the plunger to get rid of the bubbles. Then continue to fill the syringe with the correct volume of suspension as advised by your doctor. Withdraw the syringe from the vial.

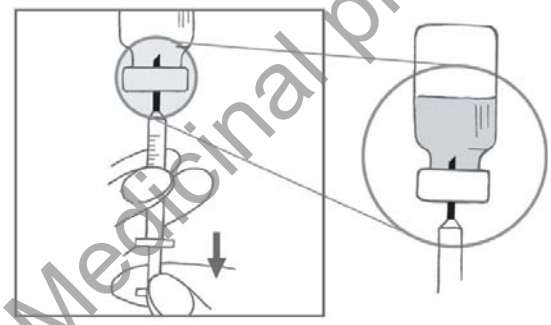

figure 9

Injecting the suspension

10. Gently tap the syringe to remove small air bubbles. Hold the syringe upright. Apply gentle pressure to the plunger until a small drop of suspension appears at the end of the needle.

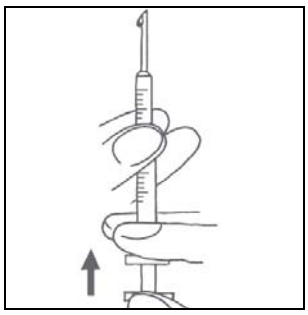

figure 10

11. Clean the injection site with an unused alcohol swab. Do not touch the needle or allow it to come into contact with any surface prior to the injection.

12. Gently pinch the skin that has been cleaned, to make a fold. Hold the fold between the thumb and the forefinger during the entire injection. Hold the syringe firmly by the finger grip. Insert the full length of the needle into the skin fold at a right angle (90 degrees) as shown in figure 12.

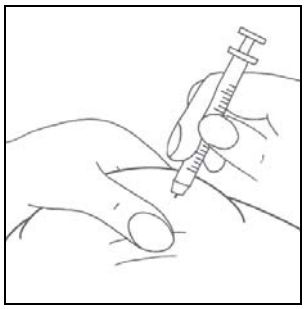

figure 12

13. Inject the suspension over a period of 5 seconds by gently pushing the plunger until the syringe is empty. Slowly release the skin during the injection. After the injection, wait a few seconds, then quickly withdraw the needle with the plunger still pushed down. Apply gentle pressure to the injection site with a dry gauze or cotton pad. If a drop of blood appears, maintain the pressure for a few moments.
Put an adhesive plaster on the injection site.

    The suspension is for immediate single use only. Any suspension remaining after the injection should be discarded.

14. Safely dispose of all used injection needles and syringes after a single use.

If you use more Somatropin Biopartners than you should

If you use more Somatropin Biopartners than you should, you should consult your doctor.
If you have used too much of this medicine, initially your blood sugar may decrease and become too low. Subsequently, it may increase and become too high. Prolonged overdose may result in a greater than normal growth of ears, nose, lips, tongue and cheekbone.

If you forget to use Somatropin Biopartners

This medicine is used once a week. It is important to use each dose at the scheduled time. If you miss a dose, contact your doctor who will help establish a new dosing schedule. Do not take a double dose to make up for a forgotten dose.

If you stop using Somatropin Biopartners
Ask your doctor for advice before stopping treatment. Interruption or early stopping of treatment with this medicine may impair the success of the therapy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects very commonly reported in adults (may affect more than 1 in 10 people) were tissue swelling due to fluid retention, mild increase in blood sugar and headache. Side effects were generally transient and mild to moderate.

Development of new tumours or reappearance of previously existing tumours has been reported during treatment with growth hormones. It is not known how often this may occur, but if you suspect that this is the case, contact your doctor since the treatment may have to be stopped.

Side effects can occur with the following frequencies:

Common, may affect up to 1 in 10 people
- virus infection known as Herpes simplex
- skin tag (a form of harmless skin growth)
- tiredness
- weakness, feeling unwell
- face swelling
- thirst
- pain, chest pain, pain at the injection site
- pain in the back, arms, legs, shoulders, bones, joints
- sleeplessness
- decreased sensation, numbness and tingling in fingers and palm of the hand due to squeezed nerve at wrist (carpal tunnel syndrome)
- dizziness, sleepiness
- muscular or bone stiffness, weakness of the muscles, muscle pain, feeling of heaviness
- inflammation of the tendons, joint swelling, joint inflammation
- reddening of the eyes, reduced vision, vertigo (a feeling of dizziness or spinning)
- increased or irregular heart rate
- high blood pressure
- nosebleed
- nausea
- increased level of bilirubin, a substance produced by the liver
- inflammation of the gall bladder
- acne, increased sweating, skin rash
- allergic skin reactions such as redness, irritation, itching
- blood in the urine
- nipple pain
- reduced function of the adrenal gland (which could show as tiredness)
- reduced function of the thyroid gland
- increased fat levels in the blood
- weight gain
- development of substances (antibodies) in the blood that bind to growth hormone
- changes in blood test results such as a change in the number of white blood cells or increased levels of insulin, sugar, sodium or certain fatty substances in the blood
- changes in liver test results
- a type of benign brain tumour called craniopharyngioma

Uncommon, may affect up to 1 in 100 people
- enlargement of the male breast

Rare, may affect up to 1 in 1,000 people
- symptoms of increased pressure in the skull such as severe and recurrent headache, visual changes, nausea and/or vomiting

Not known, frequency cannot be estimated from the available data
- a reduced response to insulin (insulin resistance)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Somatropin Biopartners

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Storage conditions of the unopened product

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

Shelf-life after reconstitution with solvent

After preparation, the product must be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Somatropin Biopartners contains

The active substance is somatropin.
- **Somatropin Biopartners 2 mg:** One vial of powder delivers 2 mg somatropin, corresponding to 6 IU. After preparation, 0.2 mL of suspension contains 2 mg somatropin (10 mg/mL).
- **Somatropin Biopartners 4 mg:** One vial of powder delivers 4 mg somatropin, corresponding to 12 IU. After preparation, 0.4 mL of suspension contains 4 mg somatropin (10 mg/mL).
- **Somatropin Biopartners 7 mg:** One vial of powder delivers 7 mg somatropin, corresponding to 21 IU. After preparation, 0.7 mL of suspension contains 7 mg somatropin (10 mg/mL).

The other ingredients are sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous and disodium phosphate anhydrous.

What Somatropin Biopartners looks like and contents of the pack

Somatropin Biopartners is a powder and solvent for prolonged-release suspension for injection. The powder is white to almost white, the solvent is a clear liquid.

- **Somatropin Biopartners 2 mg:** 2 mg (6 IU) somatropin as powder in a glass vial closed with a rubber stopper (butyl) and a yellow flip-off cap (aluminium and plastic) and 1.5 mL solvent (medium chain triglycerides) in a glass vial with a rubber stopper (butyl).
  Pack size of 4 vials of powder and 4 vials of solvent.
- **Somatropin Biopartners 4 mg:** 4 mg (12 IU) somatropin as powder in a glass vial closed with a rubber stopper (butyl) and a pink flip-off cap (aluminium and plastic) and 1.5 mL solvent (medium chain triglycerides) in glass vial with a rubber stopper (butyl).
  Pack size of 4 vials of powder and 4 vials of solvent.
- **Somatropin Biopartners 7 mg:** 7 mg (21 IU) somatropin as powder in a glass vial closed with a rubber stopper (butyl) and a light-blue flip-off cap (aluminium and plastic) and 1.5 mL solvent (medium chain triglycerides) in glass vial with a rubber stopper (butyl).
  Pack size of 4 vials of powder and 4 vials of solvent.

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This leaflet was last approved in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Package leaflet: Information for the user

Somatropin Biopartners 10 mg powder and solvent for prolonged-release suspension for injection

Somatropin Biopartners 20 mg powder and solvent for prolonged-release suspension for injection

For children and adolescents aged 2 to 18 years

somatropin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Somatropin Biopartners is and what it is used for

Somatropin Biopartners contains human growth hormone, also called somatropin. Growth hormone regulates the growth and development of cells. When it stimulates the growth of cells in the long bones of the legs and spine, it causes an increase in height.

This medicine is used to treat failure to grow normally (growth deficiency) in children and adolescents aged 2 to 18 years with insufficient secretion of growth hormone.
It is indicated in children and adolescents for long-term use.

2. What you need to know before you use Somatropin Biopartners

Do not use Somatropin Biopartners

- if you are allergic to somatropin or any of the other ingredients of this medicine (listed in section 6);
- if you have cancer;
  Tell your doctor if you have an active tumour (cancer). Tumours must be inactive and cancer

therapy complete before you can start your treatment with growth hormone. Your doctor will stop your treatment with this medicine if there is evidence of cancerous growth;
- if you are a child that has already stopped growing;
- if you are ill due to a serious heart or stomach operation;
- if you are being treated for more than one injury following a serious accident;
- if you experience sudden serious breathing problems.

Warnings and precautions

Talk to your doctor before using Somatropin Biopartners if you:
- have a hereditary disease called Prader-Willi syndrome:
  You should not be treated with this medicine unless you also have a lack of growth hormone;
- have had a tumour:
  Your doctor will examine you frequently to ensure that the tumour has not come back;
- have symptoms like severe and recurrent headache, visual changes, nausea and/or vomiting which may be due to increased pressure in the skull during growth hormone treatment;
- suffer from an organic growth hormone deficiency (lack of growth hormone due to damage to the pituitary gland or the part of the brain called the hypothalamus) or decreased secretion of pituitary gland hormones:
  Your doctor will check your levels of adrenal hormones (glucocorticoids) which may require adjustment once growth hormone therapy begins.

Monitoring during treatment

- Your doctor may check the level of sugar in your urine or blood since it may be affected by this medicine.
- You must have regular thyroid function tests as this medicine can affect the amount of thyroid hormone in the blood.
  If the thyroid is not working properly, this medicine may not work as well as it should.
- Inform the doctor if you begin to limp during treatment.
- If you have had a tumour your doctor will examine you before and regularly during treatment. This is because the doctor will stop the treatment should a tumour occur.
- If you have an abnormal curving of the spine your doctor will monitor you for worsening of this condition.

Children below 2 years of age

This medicine should not be used in infants below the age of 2 years.

Other medicines and Somatropin Biopartners

Tell your doctor or pharmacist if you are using, have recently used or are planning to use any other medicines.

In particular, inform your doctor if you are taking or have recently taken any of the following medicines. Your doctor may need to adjust the dose of Somatropin Biopartners or of the other medicines:
- corticosteroids, such as cortisone or prednisolone: medicines to reduce inflammation or immune system activity, to prevent organ transplant rejection or to treat asthma
- thyroxine: a medicine to treat reduced thyroid gland function
- insulin: a medicine to lower blood sugar levels
  The doctor will carefully monitor you during treatment as the effect of insulin may be reduced.
- oestrogen taken orally or other sex hormones
- medicines to treat epilepsy
- cyclosporine: a medicine to suppress the immune system

Pregnancy and breast-feeding

You should not use Somatropin Biopartners if you are pregnant or are trying to become pregnant. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if this medicine passes into breast milk. If you are breast-feeding only use this medicine if your doctor indicates it is clearly necessary.

Driving and using machines

Somatropin Biopartners has no or negligible effects on the ability to drive and use machines.

Important information about some of the ingredients of Somatropin Biopartners

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

3. How to use Somatropin Biopartners

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

This medicince is injected once a week.

The dose will be calculated by your doctor as described below. Individual doses may vary and your doctor will always prescribe the minimum effective dose based on your specific need.

Your dose should be checked every 6 months by your doctor.

The recommended dose is 0.5 mg of somatropin per kilogram of body weight injected once a week.

The weekly dose of 0.5 mg of somatropin per kilogram of body weight should not be exceeded due to limited experience with higher doses in children.

Somatropin Biopartners 10 mg is sufficient for use in children up to 20 kg bodyweight. Somatropin Biopartners 20 mg is sufficient for use in children up to 40 kg bodyweight. If you are heavier than 40 kg, two vials must be used.

The maximum injection volume per injection site should not exceed 1 mL. Therefore, if you weigh more than 40 kg the overall injection volume must be divided into equal parts between two injection sites, as more than 1 mL of suspension is required.

Please also see the required adjustments described in section 2, 'Other medicines and Somatropin Biopartners'.

Method of administration

After the powder is evenly mixed with the solvent provided, this medicine is injected under the skin. This means that after preparation, the suspension is injected with a short needle into the fatty skin tissue. After the injection, growth hormone is slowly released into your body over a period of about a week.

Injections should always be given on the same day of the week and at the same time of day because it is easier to remember.

If you are injecting this medicine yourself you will be shown how to prepare and give the injection. Do not inject this medicine yourself unless you have received training and you understand the procedure.

Inject the medicine as instructed by your doctor who will also tell you what dose to use and how to inject this dose with the vials you have been prescribed. Fatty tissue under the skin can shrink at the site of injection on repeated administration at the same site. To avoid this, always change the injection site between injections. This gives your skin and the area under your skin time to recover from one injection before it gets another one in the same place.

Accidental injection of this medicine into the muscle instead of under the skin may result in blood sugar levels becoming too low. Contact your doctor if this happens.

Information about self-injection of Somatropin Biopartners

Follow the instructions carefully step by step.

Collect the following items before you begin:
- supplied in the pack
  - Somatropin Biopartners vial containing active substance
  - Somatropin Biopartners vial containing 1.5 mL solvent for suspension for injection
- not supplied in the pack
  - one sterile injection syringe with 19 (19G) or wider Gauge needle to withdraw the solvent
  - one sterile injection syringe with 26 Gauge (26G) needle for the injection
  - alcohol swabs
  - dry gauze or cotton pad
  - an adhesive plaster
  - disposal box for used syringes and needles

Preparing the suspension

1. Remove the carton from the refrigerator. Wash your hands thoroughly with soap and water and dry them with a clean towel before preparing your injection. This helps to prevent infection.

2. Warm the solvent vial to room temperature by gently rolling it between your hands. Tap and shake the vial of powder to make sure the powder is moving freely.

3. Remove the protective caps from the top of both vials as seen in figure 3a. Clean the rubber stopper of both vials with an alcohol swab (figure 3b).

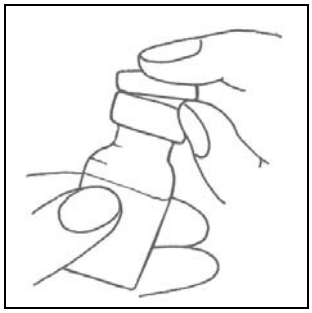

figure 3a

figure 3b

4. Use a 1 mL or 2 mL graduated syringe with a 19G or wider needle for withdrawing the solvent from its vial. Remove the needle guard and fill the syringe with a volume of air equal to the required volume of the solvent for injection, making it easier to withdraw the solvent:

   - 0.7 mL in a 1 mL graduated syringe for Somatropin Biopartners 10 mg
   - 1.2 mL in a 2 mL graduated syringe for Somatropin Biopartners 20 mg

   Insert the needle through the centre of the rubber stopper of the solvent vial and inject all of the air into the vial.

figure 4

5. Turn the vial upside down, with the syringe inside and place the tip of the needle in the solvent as seen in figure 5. Slowly withdraw the required volume of solvent.
To remove any bubbles, gently tap the syringe. Apply gentle pressure by pushing the plunger up, until all bubbles are removed from the syringe and needle. Continue to fill the syringe with the correct volume of the solvent for injection, as described in the text of figure 4 above. Withdraw the syringe needle from the vial. Do not use any remaining solvent for a second preparation!

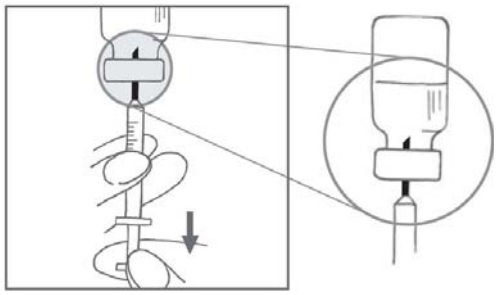

figure 5

6. Inject the entire contents of the syringe into the vial of powder, holding the syringe against the vial wall. Withdraw the syringe and discard it.

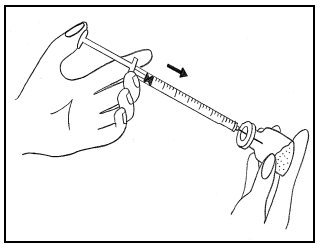

figure 6

7. Vigorously swirl the vial without touching the rubber top with your fingers until the content is completely mixed. This usually takes approximately 60 seconds but can take up to 90 seconds. Only stop swirling the vial once the suspension appears uniform, white and all the powder on the bottom is dispersed. Use immediately, as the suspension may settle if left standing.
Do not use this medicine if you notice that it cannot be properly mixed.

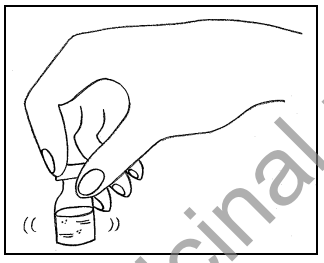

figure 7

Withdrawing the suspension

8. Clean the rubber stopper again with an unused alcohol swab.
Take a new syringe with a 26G needle. Remove the needle guard. Insert the needle straight through the centre of the vial's rubber stopper into the suspension.

figure 8

9. Turn the vial upside down, with the syringe in and place the tip of the needle in the suspension as shown in figure 9. Slowly withdraw the suspension. Because it is a thick mixture, the syringe might fill slowly. If the flow stops or bubbles appear, gently tap the syringe with your fingers. Apply gentle pressure to the plunger to get rid of the bubbles. Then continue to fill the syringe with the correct volume of suspension as advised by your doctor. Withdraw the syringe from the vial.

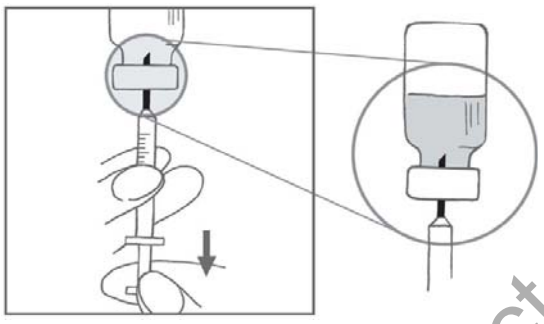

figure 9

Injecting the suspension

10. Gently tap the syringe to remove small air bubbles. Hold the syringe upright. Apply gentle pressure to the plunger until a small drop of suspension appears at the end of the needle.

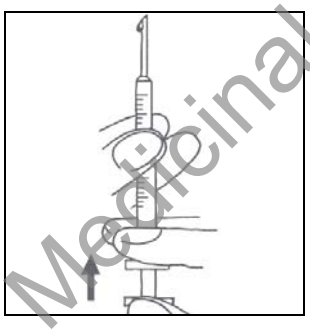

figure 10

11. Clean the injection site with an unused alcohol swab. Do not touch the needle or allow it to come into contact with any surface prior to the injection.

12. Gently pinch the skin that has been cleaned, to make a fold. Hold the fold between the thumb and the forefinger during the entire injection. Hold the syringe firmly by the finger grip. Insert the full length of the needle into the skin fold at a right angle (90 degrees) as shown in figure 12.

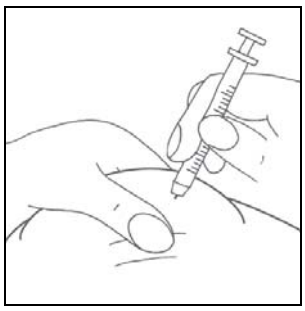

figure 12

13. Inject the suspension over a period of 5 seconds by gently pushing the plunger until the syringe is empty. Slowly release the skin during the injection. After the injection, wait a few seconds, then quickly withdraw the needle with the plunger still pushed down. Apply gentle pressure to the injection site with a dry gauze or cotton pad. If a drop of blood appears, maintain the pressure for a few moments.
Put an adhesive plaster on the injection site.

    The suspension is for immediate single use only. Any suspension remaining after the injection should be discarded.

14. Safely dispose of all used injection needles and syringes after a single use.

If you use more Somatropin Biopartners than you should

If you use more Somatropin Biopartners than you should, you should consult your doctor.
If you have used too much of this medicine, initially your blood sugar may decrease and become too low. Subsequently, it may increase and become too high. Prolonged overdose may result in a greater than normal growth of ears, nose, lips, tongue and cheekbone.

If you forget to use Somatropin Biopartners

This medicine is used once a week. It is important to use each dose at the scheduled time. If you miss a dose, contact your doctor who will help establish a new dosing schedule. Do not take a double dose to make up for a forgotten dose.

If you stop using Somatropin Biopartners

Ask your doctor for advice before stopping treatment. Interruption or early stopping of treatment with this medicine may impair the success of the therapy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects very commonly reported (may affect more than 1 in 10 people) were injection site swelling and development of substances (antibodies) in the blood that bind to growth hormone. Side effects were generally transient and mild to moderate.

Development of new tumours or reappearance of previously existing tumours has been reported during treatment with growth hormones. It is not known how often this may occur, but if you suspect that this is the case, contact your doctor since the treatment may have to be stopped.

Side effects can occur with the following frequencies:

Common, may affect up to 1 in 10 people
- tiredness or weight gain due to underactive thyroid gland
- reduced function of the adrenal gland (which may show as tiredness)
- mild blood sugar increase
- headache, lethargy (lack of energy), dizziness
- vomiting, stomach ache
- discoloration of the skin
- pain in joints, arms or legs
- pain, discoloration, swelling, hardening, reddening or feeling of warmth at the injection site
- tissue swelling
- fever
- changes in blood levels of certain hormones

Rare, may affect up to 1 in 100 people
- abnormal sensation such as prickling, tingling and itchiness
- high blood pressure

Very rare, may affect up to 1 in 1,000 people
- sleeplessness
- enlargement of the male breast

Not known, frequency cannot be estimated from the available data
- a reduced response to insulin (insulin resistance)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Somatropin Biopartners

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Storage conditions of the unopened product

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

Shelf-life after reconstitution with solvent

After preparation, the product must be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Somatropin Biopartners contains

The active substance is somatropin.

- **Somatropin Biopartners 10 mg:** One vial of powder delivers 10 mg somatropin, corresponding to 30 IU. After preparation, 0.5 mL of suspension contains 10 mg somatropin (20 mg/mL).
- **Somatropin Biopartners 20 mg:** One vial of powder delivers 20 mg somatropin, corresponding to 60 IU. After preparation, 1 mL of suspension contains 20 mg somatropin (20 mg/mL).

The other ingredients are sodium hyaluronate, egg phospholipids, sodium dihydrogen phosphate anhydrous and disodium phosphate anhydrous.

What Somatropin Biopartners looks like and contents of the pack

Somatropin Biopartners is a powder and solvent for prolonged-release suspension for injection. The powder is white to almost white; the solvent is a clear liquid.

- **Somatropin Biopartners 10 mg:** 10 mg (30 IU) somatropin as powder in a glass vial closed with a rubber stopper (butyl) and a light-green flip-off cap (aluminium and plastic) and 1.5 mL solvent (medium chain triglycerides) in glass vial with a rubber stopper (butyl).
  Pack sizes of 1 vial of powder and 1 vial of solvent and 4 vials of powder and 4 vials of solvent.
- **Somatropin Biopartners 20 mg:** 20 mg (60 IU) somatropin as powder in a glass vial closed with a rubber stopper (butyl) and a green flip-off cap (aluminium and plastic) and 1.5 mL solvent (medium chain triglycerides) in glass vial with a rubber stopper (butyl).
  Pack size of 1 vial of powder and 1 vial of solvent and 4 vials of powder and 4 vials of solvent.

Not all pack sizes may be available in your country.

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This leaflet was last approved in

Other sources of information

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