saizen® Liquid
6 mg (5.83 mg/ml),
12 mg (8 mg/ml),
20 mg (8 mg/ml)
solution for injection

NAME OF THE MEDICINAL PRODUCT
Saizen® Solution for Injection 5.83mg/ml (6mg/1.03ml)
Saizen® Solution for Injection 8mg/ml (12mg/1.50ml)
Saizen® Solution for Injection 8mg/ml (20mg/2.50ml)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each cartridge of Saizen® Solution for Injection contains Somatropin* (recombinant human growth hormone).
*produced by recombinant DNA technology in mammalian cells

PHARMACEUTICAL FORM
Solution for injection.

Clear to slightly opalescent solution with pH of 5.6-6.6 and osmolality 250-450 mOsm/kg

CLINICAL PARTICULARS
Therapeutic indications
Saizen® is indicated in the treatment of:

• growth failure in children caused by decreased or absent secretion of endogenous growth hormone.
• growth failure in girls with gonadal dysgenesis (Turner Syndrome), confirmed by chromosomal analysis.
• growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA) with a birth weight and/or length below – 2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later.
• replacement therapy in adults with pronounced growth hormone deficiency as diagnosed by a single dynamic test for growth hormone deficiency. Patients must also fulfil the following criteria:

Childhood Onset:
Patients who were diagnosed as growth hormone deficient during childhood, must be retested and their growth hormone deficiency confirmed before replacement therapy with Saizen® is started.

Adult Onset:
Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin.

Posology and method of administration
Saizen® 5.83mg/ml and Saizen® 8mg/ml are intended for multiple dose use.
Saizen® dosage should be individualised for each patient based on body surface area (BSA) or on body weight (BW).

It is recommended that Saizen® be administered at bedtime according to the following dosage:

Growth failure due to inadequate endogenous growth hormone secretion:

0.7-1.0 mg/m2 body surface area (BSA) per day or 0.025-0.035 mg/kg body weight (BW) per day by subcutaneous administration.

Growth failure in girls due to gonadal dysgenesis (Turner Syndrome):
1.4 mg/m^2 body surface area (BSA) per day or 0.045-0.050 mg/kg body weight (BW) per day by subcutaneous administration. Concomitant therapy with non-androgenic anabolic steroids in patients with Turner Syndrome can enhance the growth response.

Growth failure in short children born small for gestational age (SGA):
The recommended daily dose is 0.035 mg/kg body weight (or 1 mg/m2/day, equal to 0.1 IU/kg/day or 3 IU/m2/day) per day, by subcutaneous administration.

Duration of treatment
Treatment should be discontinued when the patient has reached a satisfactory adult height, or the epiphyses are fused.

For growth disturbance in short children born SGA, treatment is usually recommended until final height is reached. Treatment should be discontinued after the first year if height velocity SDS is below +1. Treatment should be discontinued when final height is reached (defined as height velocity < 2 cm/year), and if confirmation is required if bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Growth Hormone Deficiency in adults:
At the start of somatropin therapy, low doses of 0.15-0.3mg are recommended, given as a daily subcutaneous injection. The dose should be adjusted stepwise, controlled by Insulin-like Growth Factor 1 (IGF-1) values. The recommended final GH dose seldom exceeds 1.0mg/day. In general the lowest efficacious dose should be administered. Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are under-treated while men are over-treated. In older or overweight patients, lower doses may be necessary.

Method of administration
For administration of the solution for injection of Saizen® follow the instructions given in the package leaflet and in the instruction manual provided with the Easypod® auto-injector or aluetta pen injector.

Contra-indications
Saizen® should not be used in children in whom epiphyseal fusion occurred.

Saizen® is contraindicated in patients known to be hypersensitive to Somatropin and any of the excipients in the solution for injection.

Saizen® is contraindicated in patients with active neoplasia. Any anti-tumor therapy must be completed prior to starting treatment with Somatropin.

Saizen® should not be used in cases with evidence of any progression or recurrence of an underlying intra-cranial lesion.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Somatropin. (Regarding patients undergoing Somatropin therapy and becoming critically ill, see “Special warnings and special precautions for use“.)

Saizen® is contraindicated in patients with proliferative or pre-proliferative diabetic retinopathy.

Saizen® is contraindicated in pregnancy and lactation.

Special warnings and special precautions for use
Treatment should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of patients with growth hormone deficiency.

Patients with an intra or extracranial neoplasia in remission who are receiving treatment with growth hormone should be examined carefully and at regular intervals by the physician.

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

There is limited data on the risk of malignancies with somatotropin, patients on treatment with Saizen® should be carefully monitored.

In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

Leukemia
Some cases of leukaemia have been reported in growth hormone deficient children, untreated as well as treated with growth hormone, and might possibly represent a slightly increased incidence compared with non-growth hormone deficient children. A causal relationship to growth hormone therapy has not been established.

Insulin sensitivity
Growth Hormone administration is followed by a transient phase of hypoglycemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations. Somatropin may induce a state of insulin resistance which can result in hyperinsulinism and in some patients in hyperglycemia. To detect insulin resistance, patients should be monitored for evidence of glucose intolerance.

Saizen® should be used with caution in patients with diabetes mellitus or with a family history of diabetes mellitus. Patients with diabetes mellitus may require adjustment of their antidiabetic therapy.

Stable background retinopathy should not lead to discontinuation of Somatropin replacement therapy. In case of development of preproliferative changes and the presence of proliferative retinopathy Somatropin replacement therapy should be discontinued.

Thyroid function
During treatment with Somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In general, the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects. The effects of Somatropin on thyroid hormone levels may be of clinical relevance in patients with central subclinical hypothyroidism in whom overt hypothyroidism theoretically may develop. If hypothyroidism is diagnosed in the course of Saizen® therapy, it should be corrected.

Conversely, in patients receiving replacement therapy with thyroxine mild hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with Somatropin and after dose adjustments.

Fluid retention is expected during growth hormone replacement therapy in adults. However, these symptoms/signs are usually transient and dose dependent.

In case of persistent oedema or severe paraesthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome.

Benign intracranial hypertension
In case of severe or recurrent headache, visual problems, nausea and/or vomiting, fundoscopy for papilloedema is recommended. If papilloedema is confirmed a diagnosis of benign intracranial hypertension (or pseudotumor cerebri) should be considered and Saizen® treatment should be discontinued. At present there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial

hypertension. If growth hormone is restarted, careful monitoring for symptoms of intracranial hypertension is necessary and treatment should be discontinued if intracranial hypertension recurs.

Fundoscopic examination should be performed routinely before initiating treatment with Saizen® to exclude pre-existent papilloedema and repeated if there is any clinical suspicion. If papilloedema is confirmed by fundoscopy, Saizen® treatment should be stopped. It can be restarted at a lower dose after idiopathic intracranial hypertension has resolved which occurs rapidly when treatment is withdrawn.

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

Scoliosis
Scoliosis is known to be more frequent in some of the patient groups treated with somatropin, for example Turner syndrome. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.

Special populations
Patients with renal impairment
Somatropin clearance is known to be reduced in patients with renal impairment.

Patients with hepatic impairment
Somatropin clearance is known to be reduced in patients with hepatic impairment. However, as Saizen has not been studied in patients with hepatic impairment, the clinical significance of this finding is unknown.

Antibodies
As with all Somatropin containing products, a small percentage of patients may develop antibodies to Somatropin. The binding capacity of these antibodies is low and there is no effect on growth rate.

Testing for antibodies to Somatropin should be carried out in any patient who fails to respond to therapy.

Slipped capital femoral epiphysis is often associated with endocrine disorders such as growth hormone deficiency and hypothyroidism, and with growth spurts. In children treated with growth hormone, slipped capital femoral epiphysis may either be due to underlying endocrine disorders or to the increased growth velocity caused by the treatment. Growth spurts may increase the risk of joint-related problems, the hip joint being under particular strain during the prepubertal growth spurt.

Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in children treated with Saizen®.
In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

For SGA patients it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, increased body mass index, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

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

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

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

The injection site should be varied to prevent lipoatrophy.

Growth Hormone Deficiency in the Adult is a lifelong condition and should be treated accordingly, however experience with patients over sixty years and experience with prolonged treatment is limited.

Acute critical illness
As there is no information available on the safety of growth hormone substitution therapy in patients with acute critical illness, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

Prader-Willi Syndrome
Saizen® is not indicated for the long-term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi Syndrome, unless they also have a diagnosis of growth hormone deficiency. There have been reports of sleep apnoea and sudden death in patients after initiating therapy with growth hormone in paediatric 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.

Interaction with glucocorticoids
Initiation of growth hormone replacement may unmask secondary adrenal insufficiency in some patients by reducing the activity of 11β-hydroxysteroid dehydrogenase, type 1 (11β-HSD1), an enzyme converting inactive cortisone to cortisol and glucocorticoid replacement may be required. Initiation of somatropin in patients receiving glucocorticoid replacement therapy may lead to manifestation of cortisol deficiency. Adjustment of glucocorticoid dose may be required.

Use with oral oestrogen therapy
If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects.

Interactions with other medicinal products and other forms of interaction

Concomitant corticosteroid therapy may inhibit the response to Saizen®.
Somatropin has been reported to induce a modest reduction of serum cortisol levels in GH deficient patients receiving adrenal substitution treatment. Therefore, it is recommended to monitor serum cortisol levels in patients on corticosteroid replacement therapy in whom Somatropin therapy is started and adjust the dose of corticosteroids if necessary.
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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 on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal.

Published in vitro data indicate that growth hormone may be an inducer of cytochrome P450 3A4. The clinical significance of this observation is unknown. However, when Somatropin is administered in combination with drugs known to be metabolised by CYP P450 3A4 hepatic enzymes, it is advisable to monitor the clinical effectiveness of such drugs.

Pregnancy and lactation
Pregnancy:
For Saizen® no clinical data on exposed pregnancies are available. Thus, the risk for humans is unknown. Although animal studies do not point to a potential risk during pregnancy, Saizen® should be discontinued if pregnancy occurs.

Lactation:
It is not known if exogenous peptide hormones are excreted into breast milk but absorption of intact protein from the gastrointestinal tract of the infant is unlikely. However, as a precaution weaning is indicated before Saizen® is administered.

Effects on ability to drive and use machines
Saizen® does not interfere with the patient's ability to drive or use machinery.

Undesirable effects
Up to 10 % of patients may experience redness and itching at the site of injection.

Fluid retention is expected during growth hormone replacement therapy in adults. Oedema, joint swelling, arthralgias, myalgias and paresthesias may be clinical manifestations of fluid retention. However, these symptoms/ signs are usually transient and dose dependent.

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

Antibodies to Somatropin can form in some patients; the clinical significance of these antibodies is unknown, though to date the antibodies have been of low binding capacity and have not been associated with growth attenuation except in patients with gene deletions. In very rare instances, where short stature is due to deletion of the growth hormone gene complex, treatment with growth hormone may induce growth attenuating antibodies.

Pancreatitis has been reported in post-marketing studies during growth hormone therapy.

The adverse reactions reported below are classified according to frequency of occurrence as follows:

Very Common > 1/10
Common > 1/100 - < 1/10
Uncommon > 1/1000 - < 1/100
Rare > 1/10000 - < 1/1000
Very rare < 1/10000

Application site disorders
Common
Injection site reactions
Localized lipoatrophy, which can be avoided by varying the site of injection

Body as a whole – General disorders
Common (in adults) *Uncommon* (in children)
Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paresthesia.
Uncommon
Carpal tunnel syndrome

CNS
Common
Isolated headache, carpal tunnel syndrome (in adults)
Uncommon
Idiopathic intracranial hypertension (benign intracranial hypertension), carpal tunnel syndrome (in paediatric patients)

Endocrine Disorders
Very rare
Hypothyroidism

Musculo-skeletal disorders
Very rare
Slipped capital femoral epiphysis (Epiphysiolysis capitis femoris), or avascular necrosis of the femoral head

Metabolism disorders
Insulin resistance can result in hyperinsulinism and in rare cases in hyperglycemia.

Immune system disorders
Frequency not known: Localised and generalised hypersensitivity reactions

Reproductive system and breast disorders
Uncommon: Gynaecomastia

Overdose

No cases of acute overdosage have been reported. However, exceeding the recommended doses can cause side effects.
Overdosage can lead to hypoglycaemia and subsequently to hyperglycaemia. Moreover, Somatropin overdose is likely to cause manifestations of fluid retention.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Anterior pituitary lobe hormones and analogues, ATC code: HO1A.

Saizen® contains recombinant human growth hormone produced by genetically engineered mammalian cells.

It is a peptide of 191 amino acids identical to human pituitary growth hormone with respect to aminoacid sequence and composition as well as peptide map, isoelectric point, molecular weight, isomeric structure and bioactivity.

Growth hormone is synthesised in a transformed murine cell line that has been modified by the addition of the gene for pituitary growth hormone.

Saizen® is an anabolic and anticatabolic agent which exerts effects not only on growth but also on body composition and metabolism. It interacts with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes and hematopoietic cells. Some, but not all of its effects are mediated through another class of hormones known as somatomedins (IGF-1 and IGF-2).

Depending on the dose, the administration of Saizen® elicits a rise in IGF-1, IGFBP-3, non-esterified fatty acids and glycerol, a decrease in blood urea, and decreases in urinary nitrogen, sodium and potassium excretion. The duration of the increase in GH levels may play a role in determining the magnitude of the effects. A relative saturation of the effects of Saizen® at high doses is probable. This is not the case for glycemia and urinary C-peptide excretion, which are significantly elevated only after high doses (20 mg).

In a randomised clinical trial, three years treatment of prepubertal short children born SGA with a dose of 0.067 mg/kg/day resulted in a mean gain of +1.8 height-SDS. In those children who did not receive treatment beyond 3 years, part of the treatment benefit was lost, but the patients retained a significant gain of +0.7 height-SDS at final height ($p<0.01$ compared to baseline). Patients who received a second treatment course after a variable period of observation experienced a total gain of +1.3 height-SDS ($p=0.001$ compared to baseline) at final height. (The mean cumulative treatment duration in the latter group was 6.1 years). The gain in height-SDS (+1.3 ± 1.1) at final height in this group was significantly ($p<0.05$) different from the gain in height-SDS obtained in the first group (+0.7±0.8) that received only 3.0 years of treatment on average.

A second clinical trial investigated two different dose regimens over four years. One group was treated with 0.067 mg/kg/day for 2 years and then observed without treatment for 2 years. The second group received 0.067mg/kg/day in the first and third year and no treatment in the second and fourth year. Either treatment regimen resulted in a cumulative administered dose of 0.033/mg/kg/day over the four-year study period. Both groups showed a comparable acceleration of growth and a significant improvement of +1.55 ($p<0.0001$) and + 1.43 ($p<0.0001$) height-SDS respectively at the end of the four year study period. Long-term safety data are still limited.

Pharmacokinetic properties

The pharmacokinetics of Saizen® are linear at least up to doses of 8 IU (2.67 mg). At higher doses (60 IU/20 mg) some degree of non-linearity cannot be ruled out, however with no clinical relevance.
Following IV administration in healthy volunteers the volume of distribution at steady-state is around 7 L, total metabolic clearance is around 15 L/h while the renal clearance is negligible, and the drug exhibits an elimination half-life of 20 to 35 min.

Following single-dose SC and IM administration of Saizen®, the apparent terminal half-life is much longer, around 2 to 4 hours. This is due to a rate limiting absorption process.

Maximum serum growth hormone (GH) concentrations are reached after approximately 4 hours and serum GH levels return to baseline within 24 hours, indicating that no accumulation of GH will occur during repeated administrations.

The absolute bioavailability of both routes is 70-90 %.

Saizen solutions for injection (5.83 and 8.00 mg/ml) administered subcutaneously have been shown to be bioequivalent versus the 8 mg freeze-dried formulation.

Preclinical safety data
The local tolerability of Saizen solution for injection was shown to be good and suitable for SC administration, when injected in animals at a concentration of 8.00 mg/ml and volumes of 1 ml/site.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Reproductive toxicology studies do not indicate any adverse effect on fertility and reproduction, despite administration of doses sufficiently high to produce some pharmacological effects on growth.

List of excipients
Sucrose
Poloxamer 188
Phenol
Citric Acid
Citrate buffer

Incompatibilities
No incompatibilities of Saizen® with other pharmaceutical preparations are known at present.

Shelf life
2 years.
Once opened, the product may be stored for a maximum of 28 days in a refrigerator (2°C to 8°C), of which up to 7 days can be at or below 25°C.

Special precautions for storage
Store in a refrigerator ($2^{o}C – 8^{o}C$). Do not freeze. Store in the original package to protect from light. When containing a cartridge of Saizen®, the easypod auto-injector or the aluetta pen injector has to be stored in a refrigerator ($2^{o}C – 8^{o}C$) for a maximum of 28 days, of which up to 7 days can be outside of a refrigerator at or below 25°C.

Special precautions for disposal and other handling
The cartridge containing the solution for Saizen 5.83mg/ml or Saizen 8mg/ml is for use only with the easypod auto-injector or the aluetta pen injector.

The aluetta pen injectors and Saizen cartridges are available in several presentations. Each aluetta pen injector is colour coded and must only be used with the matching colour coded Saizen cartridge to give the correct dose. The aluetta pen injector 6 (blue) must be used with the cartridge containing 6 mg somatropin (blue).

The solution for injection should be clear to slightly opalescent with no particles and without visible signs of deterioration. If the solution contains particle, it must not be injected.

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

Package quantities
Saizen® 5.83 mg/ml solution for injection is available in the following pack sizes:
Pack of 1 cartridge, each containing 1.03 ml solution (6 mg somatropin).
Pack of 5 cartridges, each containing 1.03 ml solution (6 mg somatropin)

Saizen® 8 mg/ml solution for injection is available in the following pack sizes:
Pack of 1 cartridge, each containing 1.50 ml solution (12 mg somatropin).
Pack of 5 cartridges, each containing 1.50 ml solution (12 mg somatropin).
Pack of 1 cartridge, each containing 2.50 ml solution (20 mg somatropin).

Pack of 5 cartridges, each containing 2.50 ml solution (20 mg somatropin).

Not all pack sizes may be marketed.

Manufacturer:
Merck Serono S.p.A.
Via delle Magnolie 15 (loc. frazione Zona Industriale)
70026 - Modugno (BA), Italy

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