Merck Serono

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saizen® 8 mg click.easy®

NAME OF THE MEDICINAL PRODUCT

Saizen® 8 mg click.easy®, powder and solvent for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

.Each vial of Saizen® 8 mg click.easy® contains Somatropin* (recombinant human growth hormone).
*produced by recombinant DNA technology in mammalian cells.
Reconstitution with the contents of the bacteriostatic solvent cartridge gives a concentration of 5.83 mg per ml.

PHARMACEUTICAL FORM

Powder and solvent for solution for injection

CLINICAL PARTICULARS

Therapeutic indications

Saizen is indicated in the treatment of:

Children and adolescents:
- 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.
- Retarded growth in children born small for their gestational age defined as follows:
  - present height < -2.5 SDS and the SDS of the adjusted height of the parents is <-1,
  - weight and/or height at birth < -2 SDS, in children who have not reached their normal growth rate by the age of 4 years or more (i.e. with a growth rate < 0 SDS in the course of the last year).

Adults:
- 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® 8 mg click.easy® is intended for multiple dose use.

Saizen® dosage should be individualised for each patient based on body surface area (BSA) or on body weight (BW).

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

Children and adolescents:
Saizen dosage should be individualised for each patient based on body surface area or on body weight.
- **Growth failure due to inadequate endogenous growth hormone secretion:**
  0.7-1.0 mg/m² body surface area per day or 0.025-0.035 mg/kg body weight per day by subcutaneous administration.
- **Growth failure in girls due to gonadal dysgenesis (Turner Syndrome):**

  1.4 mg/m² body surface area per day or 0.045-0.050 mg/kg body weight 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.

Adults:

- Growth hormone deficiency in adults
  At the start of somatropin therapy, low doses of 0.15-0.3 mg 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 1.0 mg/day. In general the lowest efficacious dose should be administered. In older or overweight patients, lower doses may be necessary.

Method of administration

For administration of solution for injection of Saizen® 8 mg click.easy® follow the instructions given in the package leaflet and in the instruction manual provided with each one.click® autoinjector, Easypod® auto-injector or cool.click® needle-free auto-injector. See also section under Instructions for use/handling.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

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

Somatropin must not be used in case of proliferative or preproliferative diabetic retinopathy

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.

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.

Special warnings and 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.

The maximum recommended daily dose should not be exceeded (Please see section Posology and method of administration).

Neoplasm
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.

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.

Prader-Willi syndrome
Somatropin 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 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.

Leukaemia
Leukaemia has been reported in a small number of growth hormone deficiency 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.

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

Retinopathy
Stable background retinopathy should not lead to discontinuation of somatropin replacement therapy.

Thyroid function
Growth hormone increases the extra thyroid conversion of T4 to T3 and may, as such, unmask incipient hypothyroidism. Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

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 if appropriate, 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 treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

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

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
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

Children born small for gestational age
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.

Fluid retention
Fluid retention is expected during growth hormone replacement therapy in adults.

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

Acute critical illness
In all patients developing acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

General
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.

Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth hormone.

In addition, 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. Initiation of somatropin in patients receiving glucocorticoid replacement therapy may lead to manifestation of cortisol deficiency. Adjustment of glucocorticoid dose may be required.

Because oral oestrogens may reduce the serum IGF-1 response to somatropin treatment, patients receiving oral oestrogen replacement may require greater somatropin dosages.

Data from an interaction study performed in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P 450 3A4 (e.g. sex

steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Fertility, pregnancy and lactation

Pregnancy:
From the reproductive studies performed in animals with somatropin containing products, there is no evidence of an increased risk of adverse reactions for the embryo or foetus. (see Preclinical safety data). Therefore, somatropin containing products are not recommended during pregnancy and in woman of childbearing potential not using contraception.

Breasfeeding
There have been no clinical studies conducted with somatropin in breast-feeding women. It is not known whether somatropin is excreted in human milk. Therefore caution should be exercised when somatropin is administered to breast-feeding women.

Fertility
Non clinical toxicity studies showed that recombinant human growth hormone did not induce adverse effect on male and female fertility. (See section Preclinical safety data)

Effects on ability to drive and use machines

Somatropin-containing products have no influence on the ability to drive and use machines.

Undesirable effects

Up to 10 % of patients may experience redness and itching at the site of injection, particularly when the subcutaneous route is used.

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~~ a small percentage of patients; 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.

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

The following definitions apply to the frequency terminology used hereafter: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Very rare	Frequency not known
Nervous system disordes	(solated) Headache, carpal tunnel syndrome (in adults)	Idiopathic intracranial hypertension (benign intracranial hypertension), carpal tunnel syndrome (in children).		
Musculoskeletal and connective tissue disorders			capital femoral epiphysis (Epiphysiolysis capitis femoris), or avascular necrosis of the femoral head	
Immune system disorders				Localised and generalised hypersensitivity reactions
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders	In adults: Fluid retention, peripheral oedema, stiffness, arthralgia, myalgia, paresthesia	In children: Fluid retention, peripheral oedema, stiffness, arthralgia, myalgia, paresthesia		Insulin resistance can result in hyperinsulinism and in rare cases in hypergly cemia
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Injection site reactions, /localised lipoatrophy, which can be avoided by varying the site of injection			
Gastrointestinal disorders				Pancreatitis

Overdose

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

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues, ATC code: H01AC01.

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 glycaemia and urinary C-peptide excretion, which are significantly elevated only after high doses (20 mg).

In a randomized clinical trial, three years treatment of pre-pubertal 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 0.067 mg/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 intravenous 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 subcutaneous and ~~IM~~ intramuscular 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.

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

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

Saizen solutions for injection (5.83 and 8 mg/ml) administered subcutaneously have been shown to be equivalent 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~~ subcutaneous administration, when injected in animals at a concentration of 8 mg/ml and volumes of 1 ml/site.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. Formal carcinogenicity bioassays were not performed. This is justified, given the proteinous nature of the drug substance and the negative outcome of the genotoxicity testing. The potential effects of recombinant human growth hormone on the growth of pre-existing tumours have been evaluated through *in vitro* and *in vivo* experiments which have shown that recombinant human growth hormone is not expected to cause or stimulate tumours in patients. 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.

Incompatibilities

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

Shelf life

3 years.

After reconstitution, the product may be stored for a maximum of 28 days in a refrigerator (2°C to 8°C).

Special precautions for storage

Do not store above 30°C. Do not freeze. Store in the original package.

For storage conditions of the reconstituted medicinal product, see Shelf life.

When containing a cartridge of reconstituted Saizen, the easypod have to be stored in a refrigerator (2°C-8°C).

Package quantities

Saizen® 8 mg click.easy® is available in the following pack sizes:
1 vial of Saizen® 8 mg product and 1 cartridge of bacteriostatic solvent pre-assembled in 1 reconstitution device (click.easy®) comprising of 1 device housing and 1 sterile transfer cannula.

Instructions for use/handling

The cartridge containing the reconstituted solution of Saizen® 8 mg click.easy® is for use only with the one.click® auto-injector, Easypod® auto-injector or the cool.click® needle-free auto-injector.

For administration of Saizen® 8 mg click.easy® follow the instructions given in the package leaflet and in the instruction manual provided with each one.click® auto-injector, Easypod® auto-injector or the cool.click® needle-free auto-injector.

The powder for solution for injection must be reconstituted with the enclosed bacteriostatic solvent (0.3% (w/v) metacresol in water for injections) for parenteral use, using the click.easy® reconstitution device. The reconstituted solution for injection should be clear with no particles. If the solution contains particles, it must not be injected.

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

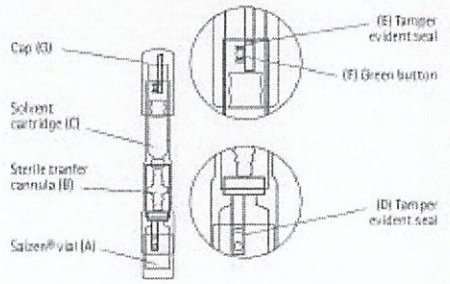
Important information:

Patients should be thoroughly instructed in the reconstitution procedure.
For young children, the reconstitution process should be supervised by an adult.

For administration of Saizen® 8 mg click.easy® please read the following instructions carefully

Detailed pictural instructions for use are provided in a separate leaflet in this box.

Please consult your doctor, nurse or pharmacist, if you have any questions concerning the reconstitution process.



- Make sure the click.easy® is complete by checking that the Saizen® vial (a), the sterile transfer cannula (b) and the solvent cartridge (c) are present.
- Check that the tamper evident seals on the click easy®housing (d) and on the cap (e) are not broken. If either of the temper evident seals are broken return it to your pharmacist or doctor.
- Place all elements needed for the preparation of the solution on a clean surface.
- Wash your hands with soap and water

How to prepare your solution of Saizen® 8 mg click.easy® :

1. Place the click.easy® reconstitution device vertically on a flat surface with the vial at the bottom and the cap (g) facing upward.
2. Push the cap down until it will go no further. (Note : The tamper evident seal on the click.easy® housing is now broken).
3. Turn slightly the cap clockwise until the green button (f) is positioned in the vertical opening.
4. Continue pushing the cap down very slowly until it will go no further to transfer the solvent from the cartridge into the vial (Note : the temper evident seal on the cap is now broken). It is important to push slowly to prevent foam to appear in the vial. Check that all the solvent has been transferred into the vial.
5. Dissolve the power with the solvent by gently swiring the click.easy® (Note : Aviod vigorous shaking to prevent creation of foam. Let the solution stand until the power is completely dissolved.
6. Turn the click.easy® upside down (vial on top). Push the cap up until it will go no further and subsequently pull the cap slowly downwards until the solution is completely dawn back into the cartridge.
   Check that no more than one or two drops of solution remain in the vial.
   If there are more than one or two drops of solution remain in the vial. Slowly push the cap up until some of solution is back in the vial and gently tap the click.easy®. Then draw the solution slowly again back into the cartridge.
   Remove any excess air that has been drawn into the cartridge by pushing slowly the cap up until no air is visible in the cartridge.
   (Note : Avoid pulling the cap down too fast, as this will draw air into the cartridge).
7. Keeping the click.easy® in this position (vial on the top) unscrew the cap and remove it.
   Still keeping the same position (vial on the top) remove the cartridge containing the reconstituted solution for injection from click.easy®.
8. Carefully peel off the outer label using the tab provided. Write the reconstitution date on the transparent inner label on the cartridge.
   Discard the click.easy® safely in accordance with your local requirements.
   The cartridge containing the reconstituted solution of Saizen® is now ready your one click® auto-injector, Easypod® auto-injector or cool.click® needle free auto-injector.
   NOTE : For instructions on how to load the cartridge into the one click® auto-injector, Easypod® auto-injector or how to use the cool.click® needle free auto-injector and inject the reconstituted solution of Saizen®, please read the instruction manual provided with your one.click® auto-injector, Easypod® auto-injector or cool.click® needle-free auto-injector.
   Injection should be given in different parts of your body. Do not use any areas in which you feel lumps. Firm knots, depressions, or pain : talk to your doctor or healthcare prefessional about anything you find.
   Clean the skin at the injection site with soap and water.

HARUS DENGAN RESEP DOKTER
On Medical Prescription Only

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Manufactured by:
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Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

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