IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0285/005/002
Case No: 2075212

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Serono Limited

Bedfont Cross, **Stanwell Road**, **Feltham**, **Middlesex**, **TW14 8NX**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Saizen 3.33mg powder and solvent for solution for injection.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/05/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Saizen 3.33 mg powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Saizen 3.33 mg contains somatropin* (recombinant human growth hormone).
*produced by recombinant DNA technology in mammalian cells

After reconstitution with the enclosed solvent, each vial shall contain ≥ 0.67 mg of Saizen/ml.

Excipients: 5 mg mannitol
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection
Appearance of the powder: white lyophilised powder.
Appearance of the solvent: clear colourless solution.
The pH of the reconstituted solution is 7.4 – 8.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Saizen is indicated in the treatment of:

Children:
- 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 failure in prepubertal children due to chronic renal failure (CRF).
- 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.

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.

4.2 Posology and method of administration

Benzyl alcohol as a preservative in bacteriostatic sodium chloride solution may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates. Saizen may be reconstituted with Sodium Chloride Injection BP or Sterile Water for Injections for immediate use when administering to children under 3 years of age.

Saizen 3.33 mg 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).

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

Children and adolescents:

- *Growth failure due to inadequate endogenous growth hormone secretion:*

  0.7-1.0 mg/m^2 body surface area (BSA) per day or 0.025-0.035 mg/kg body weight (BW) per day by subcutaneous or intramuscular 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 prepubertal children due to chronic renal failure (CRF):*

  1.4 mg/m^2 body surface area (BSA), approximately equal to 0.045-0.050 mg/kg body weight (BW), per day by subcutaneous administration.
- *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/m^2/day, equal to 0.1 U/kg/day or 3 IU/m^2/day) per day, by subcutaneous administration.

  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 1.0mg/day. In general the lowest efficacious dose should be administered. In older or overweight patients, lower doses may be necessary.

The powder for solution for injection should be used with the enclosed solvent for parenteral use. The reconstituted solution for injection should be clear with no particles. For instructions for preparation, please see *section 6.6.*

4.3 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.

Any evidence of active malignant tumours. Intracranial neoplasm must be inactive and antitumor therapy should be completed prior to institution of therapy.
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.

In children with chronic renal disease, treatment with somatropin should be discontinued at renal transplantation.

4.4 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.

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.

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 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 predisposing 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.

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
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 papille oedema is recommended. If papille oedema 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

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.

Patients with growth failure due to chronic renal failure should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy and it is uncertain whether these problems are affected by growth hormone therapy. X-rays of the hip should be obtained prior to initiating therapy.

In children with chronic renal failure, renal function should have decreased to below 50% of normal before therapy is instituted. To verify the growth disturbance, growth should have been followed for a year before institution of therapy. Conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism and nutritional status for one year prior to the treatment) should have been established and should be maintained during treatment. Treatment should be discontinued at the time of renal transplantation.

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 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.

The injection site should be varied to prevent lipoatrophy.

Benzyl alcohol as a preservative in bacteriostatic sodium chloride solution may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates. Saizen may be reconstituted with Sodium Chloride Injection BP or Sterile Water for Injections for immediate use when administering to children under 3 years of age.
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

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

4.5 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.

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

4.6 Pregnancy and lactation

Pregnancy:
Animal studies are insufficient and/or animal data is not available with regard to effects on pregnancy, embryofoetal development, parturition or postnatal development *(See section Preclinical safety data 5.3)* No clinical data on exposed pregnancies are available.Therefore, somatropin containing products are not recommended during pregnancy and in woman of childbearing potential not using contraception

Lactation:
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.

4.7 Effects on ability to drive and use machines

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

4.8 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 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.

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.

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

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Very rare (<1/10,000)	Frequency unknown
Nervous system disorders		Idiopathic intracranial hypertension (benign intracranial hypertension) Carpal tunnel syndrome		(Isolated) headache
Musculoskeletal and connective tissue disorders			Slipped capital femoral epiphysis (Epiphysiolysis capitis femoris), or avascular necrosis of the femoral head	
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 hyperglycemia.
General disorders and administration site conditions	Injection site reactions: Localized lipoatrophy, which can be avoided by varying the site of injection			

4.9 Overdose

No cases of acute overdose has 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 glycemia 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.

5.2 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 %.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, 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 r-hGH on the growth of pre-existing tumours have been evaluated through i*n vitro* and *in vivo* experiments which have shown that r-hGH 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
- Mannitol, Disodium phosphate dihydrate, Sodium dihydrogen phosphate monohydrate

Solvent:
- sodium chloride (0.9 % w/v) and benzyl alcohol (0.9 % w/v, as preservative) solution for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

2 years.
After reconstitution, the product may be stored for a maximum of 7 days in a refrigerator (2°C-8°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C) in the original package in order to protect from light.
For storage conditions of the reconstituted medicinal product, *see section 6.3*
Store the reconstituted product in a refrigerator (2°C-8°C) in the original package in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

The 10 ml vials containing 3.33 mg of powder and the 5 ml vials containing 5 ml of solvent are of neutral glass (Type I). The vials are closed by rubber stoppers.

Saizen 3.33 mg is available in the following pack sizes:
1 vial of SAIZEN 3.33 mg product and 1 vial of bacteriostatic solvent.
5 vials of SAIZEN 3.33 mg product and 5 ampoules of bacteriostatic solvent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

To reconstitute Saizen, inject 1 ml of the bacteriostatic solvent into the vial of Saizen 3.33 mg aiming the liquid against the glass wall. Swirl the vial with a gentle rotary motion until the content is dissolved completely. Avoid vigorous shaking. Discard any unused solvent.

Benzyl alcohol as a preservative in bacteriostatic sodium chloride solution may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates. Saizen may be reconstituted with Sodium Chloride Injection BP or Sterile Water for Injections for immediate use when administering to children under 3 years of age.

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

7 MARKETING AUTHORISATION HOLDER

Serono Limited
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Feltham
Middlesex
TW14 8NX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0285/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1992
Date of last renewal: 12 April 2009

10 DATE OF REVISION OF THE TEXT

April 2010