SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Saizen 5.83 mg/ml solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each cartridge contains 1.03 ml solution (6 mg somatropin*).
*recombinant human growth hormone, produced by recombinant DNA technology in mammalian cells

One ml of solution contains 5.83 mg somatropin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge.
Clear to slightly opalescent solution with pH of 5.6-6.6 and osmolality 250-450 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 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.
- 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

Saizen 5.83 mg/ml is intended for multiple dose use in an individual patient.

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/m^2 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/m^2 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 prepubertal children due to chronic renal failure (CRF):
  1.4 mg/m^2 body surface area per day, approximately equal to 0.045-0.050 mg/kg body weight 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) 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 growth hormone dose seldom exceeds 1.0 mg/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 therapy are under-treated while men are over-treated.
In older or overweight patients, lower doses may be necessary.

Patients with renal or hepatic impairment:
Currently available data are described in section 5.2 but no recommendation on a posology can be made.

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 selected injector: cool.click needle-free auto-injectors, easypod auto-injector or aluetta pen injector.

Intended users of easypod are primarily children starting from the age of 7 up to adults. Use of the devices by children should always be made under adult's supervision.

For instructions for handling please see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 antitumour therapy must 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.

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.

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

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, funduscopy 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.

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.

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.

Growth failure due to chronic renal failure
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.

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-Russell 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.

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 (see section 4.5).

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 (see section 4.5).

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.

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

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.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).

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 P450 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available. 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 section 5.3). However, somatropin containing products are not recommended during pregnancy and in woman of childbearing potential not using contraception.

Breastfeeding
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 somatropin did not induce adverse effects on male and female fertility (see section 5.3).

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.

Fluid retention is expected during growth hormone replacement therapy in adults. Oedema, joint swelling, arthralgias, myalgias and paraesthesias 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 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 disorders	Headache (isolated), carpal tunnel syndrome (in adults)	Idiopathic intracranial hypertension (benign intracranial hypertension), carpal tunnel syndrome (in children)		
Musculoskeletal and connective tissue disorders			Slipped 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, paraesthesia	In children: Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paraesthesia		Insulin resistance can result in hyperinsulinism and in rare cases in hyperglycaemia
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

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 HPRA Pharmacovigilance Earlsfort Terrace, IRL – Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.hpra.ie email: medsafety@hpra.ie

4.9 Overdose

Exceeding the recommended doses can cause side effects. Overdose 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

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 growth hormone 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 after high doses (20 mg).

In a randomised 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 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 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 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 bioequivalent versus the 8 mg freeze-dried formulation.

Renal impairment
Somatropin clearance is known to be reduced in patients with renal impairment. However, the clinical significance of this finding is unknown.
For prepubertal children with growth failure due to chronic renal failure a specific posology is recommended (see section 4.2).

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.

5.3 Preclinical safety data

In animal studies, Saizen solution for injection was shown to be very well tolerated locally when administered subcutaneously in animals at a concentration of 8 mg/m1 and volumes of 1 ml/site. Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. Formal carcinogenicity studies 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 somatropin on the growth of pre-existing tumours have been evaluated through i*n vitro* and *in vivo* experiments including rats at doses of 15 mg/kg/day (over 120 times the usual maximum daily clinical dose in adults and 60 times in children) which have shown that recombinant human growth hormone is not expected to cause or stimulate tumours in patients.
Reproductive toxicology studies performed in rats and rabbits at doses up to 3.3 mg/kg/day (over 25 times the usual maximum daily clinical dose in adults and 14 times in children) did not indicate adverse effects on embryo-foetal development nor on the F1 generation development or fertility. The fertility of adult male and female rats was not impaired.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Poloxamer 188
Phenol

Citric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

18 months

Chemical, physical and microbiological in-use stability has been demonstrated for a total of 28 days at 2°C to 8°C, of which up to 7 days can be at or below 25°C.
Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store the unused Saizen cartridge in a refrigerator (2°C-8°C). Do not freeze. Store in the original package to protect from light.

After first injection, the Saizen cartridge, the easypod auto-injector containing the Saizen cartridge or the aluetta pen injector containing the Saizen cartridge has to be stored in a refrigerator (2°C-8°C) for a maximum of 28 days, of which up to 7 days can be outside of a refrigerator at or below 25°C (see section 6.3). When stored outside of the refrigerator for up to 7 days, the Saizen cartridge must be returned to the refrigerator and used within 28 days after first injection.
When using the easypod auto-injector or the aluetta pen injector, the cartridge is kept in the device.
The cool.click needle-free auto-injector should be stored outside of a refrigerator always separately from the Saizen cartridge. Protect the used cartridge from light.

6.5 Nature and contents of container

The container is a colourless type I glass cartridge with closure consisting of a bromobutyl rubber plunger stopper and an aluminium crimp cap with a bromobutyl rubber single inlay. The glass cartridge containing 6 mg somatropin is marked with a coloured label (blue).

Saizen 5.83 mg/ml solution for injection in cartridge 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)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridge containing the solution of Saizen 5.83 mg/ml is for use only with the cool.click needle-free auto-injectors, 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).

For storage of injectors containing a cartridge, see section 6.4.

The solution for injection should be clear to slightly opalescent with no particles and without visible signs of deterioration. 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.

7. MARKETING AUTHORISATION HOLDER

Merck Serono (Ireland) Limited

4045 Kingswood Road

Citywest Business Campus

Dublin 24

Ireland

8. MARKETING AUTHORISATION NUMBER

PA 2286/6/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 2011
Date of latest renewal: 29 October 2015

10. DATE OF REVISION OF THE TEXT

08/2019

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1 OR 5 CARTRIDGES

1. NAME OF THE MEDICINAL PRODUCT

Saizen 5.83 mg/ml solution for injection in cartridge
Somatropin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 5.83 mg somatropin
Each multidose cartridge contains 1.03 ml solution (6 mg somatropin)

3. LIST OF EXCIPIENTS

Other ingredients: Sucrose, poloxamer 188, phenol, citric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge
1 cartridge of 1.03 ml (containing 6 mg somatropin)
5 cartridges of 1.03 ml (containing 6 mg somatropin)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before 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 first injection use within 28 days.

9. SPECIAL STORAGE CONDITIONS

Store unused cartridge in a refrigerator (2°C-8°C) in the original package. After first injection, store at 2°C to 8°C for a maximum of 28 days, of which up to 7 days can be at or below 25 °C. Protect from light. 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

Merck Serono (Ireland) Limited
4045 Kingswood Road
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PA 2286/6/1

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Saizen 6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SAIZEN 5.83 MG/ML CARTRIDGE LABEL

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

Saizen 5.83 mg/ml solution for injection
Somatropin
Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 mg cartridge

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Saizen 5.83 mg/ml solution for injection in cartridge
somatropin

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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Saizen is and what it is used for

Saizen is a growth hormone. Saizen's main action is to increase growth in children and adolescents and to treat adults with growth hormone deficiency.

The growth hormone (somatropin) contained in Saizen is almost the same as human's natural growth hormone except that it is made outside the body by a process called "recombinant DNA technology" (genetic engineering).

Saizen is used:

In children and adolescents:
- in the treatment of children with short stature who have failed to grow because their body produces no growth hormone or insufficient levels of growth hormone
- in the treatment of girls who have failed to grow due to gonadal dysgenesis (also referred to as Turner syndrome), confirmed by a test on the chromosomes
- in the treatment of pre-pubertal children who have failed to grow due to chronic renal failure, a condition in which kidneys are damaged
- in the treatment of growth problems in children who were born small and who have not reached normal height by the age of 4 years or later.

In adults:
- in the treatment of adults with a marked lack of growth hormone (growth hormone deficiency). This therapy is given to adults who have a serious growth hormone deficiency that has been medically diagnosed by a test.

The doctor or pharmacist will be able to explain why this medicine has been given to you or to your child.

2. What you need to know before you use Saizen

Do not use Saizen
- If you (or your child) are allergic (hypersensitive) to somatropin or any of the other ingredients of this medicine (listed in section 6).
- If you have been told that your child's bones have stopped growing and that he/she has therefore reached his/her final height.
- If you have an active tumour (cancer). Tumours must be inactive and you must have finished your anti-tumour treatment before you start your treatment with Saizen.
- If you (or your child) have diabetes and are suffering from an associated eye disease (proliferative or preproliferative diabetic retinopathy).
- If you or your child have an acute critical illness, suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions.

Treatment with Saizen has to be stopped in children with chronic kidney disease at time of kidney transplantation.

Warnings and precautions
Talk to your doctor before using Saizen.

Saizen therapy should be carried out under regular guidance of a doctor who is experienced in the diagnosis and management of patients with growth hormone deficiency.

Shortly after Saizen is given, you (or your child) may feel shaky or light-headed due to low blood sugar levels. These feelings will quickly disappear. Your (or your child's) blood sugar levels may then rise above normal 2-4 hours after administration. Since treatment with growth hormone can alter how your body handles sugar, your (or your child's) sugar levels will be tested regularly by a doctor. Somatropin may cause your (or your child's) blood sugar to increase.

If you (or your child) are diabetic or a member of your family has diabetes, your doctor will monitor closely your blood sugar level and may adjust the treatment for diabetes while you are being treated with Saizen.

Please be aware that you may need regular eye tests after having this medicine.

Saizen may affect how your thyroid works. Your doctor may test your blood for levels of thyroid hormones and prescribe another hormone if you (or your child) are found to have developed a lack of thyroid hormone.

If you (or your child) are using corticosteroids, you should consult your doctor regularly, as you may need adjustment of your corticosteroid or your Saizen dose.

Saizen may cause fluid retention in adult patients. This may appear as swelling and joint or muscle pain. If you feel these symptoms tell your doctor who may decide to adjust your dose of Saizen.

If you have had a tumour in your childhood and were treated with Saizen, there is an increased risk to develop a new tumour. If in the past you (or your child) have had a condition affecting the brain, e.g. a tumour, the doctor will examine you (or your child) regularly to check that this has not come back again.

Rarely Saizen may cause an inflammation of the pancreas, which causes severe pain in the abdomen and back. Please consider this especially if your child suffers from stomachache and contact your doctor.

An increase in sideways curvature of the spine (scoliosis) may progress in any child during rapid growth. During treatment with Saizen, your doctor will check you (or your child) for signs of scoliosis.

Some patients may develop swelling of the brain, while taking Saizen. If you (or your child) suffer from a bad or recurrent headache, problems with your eyesight, feel sick (nausea) and/or being sick (vomiting), contact your doctor immediately. In this case it may be necessary to stop the growth hormone treatment, although treatment may be re-started at a later date. If the symptoms of brain swelling come back, treatment with Saizen should be discontinued.

When the medicine is injected into the same place over a long period of time, it can cause damage to this area. It is therefore important to keep changing the injection site. Your doctor or pharmacist can speak to you about which parts of the body should be used (see section 3 How to use Saizen).

Some children with growth hormone deficiency have developed leukaemia (increased number of white blood cells), whether or not they have received treatment with growth hormone. However there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposing factors. No cause and effect relationship with growth hormone treatment has been proven.

Hip problems may occur more commonly in children with hormone or kidney problems. If your child has chronic renal failure, which can occur when kidneys are damaged, he or she should be examined periodically for evidence of bone disease. It is uncertain whether the bone disease in children with hormone or kidney problems is affected by growth hormone therapy. X-rays of the hip should be obtained prior to initiating therapy. If your child develops a limp or complains of hip or knee pain while being treated with Saizen, tell your doctor.

Treatment with Saizen will be stopped in children with chronic kidney failure at the time of kidney transplant.

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.

Growth hormone should generally not be used by people who are seriously ill.

If you do not respond to the therapy with Saizen, you may have developed antibodies to growth hormone. Your doctor will conduct appropriate tests to determine this.

If you are over 60 years old or if you are taking Saizen for a long time you should be examined more frequently by your doctor. As there is less experience both in the treatment of older people and in prolonged treatment with Saizen, special care is required.

Other medicines and Saizen
Tell your doctor or pharmacist if you (or your child) are using, have recently used or might use any other medicines.

If you (or your child) are using corticosteroids, it is important to tell the doctor or pharmacist. These medicines could interact with Saizen and therefore your doctor may need to adjust the dose of these medicines or your Saizen dose. Corticosteroids are used to treat several illnesses including asthma, allergies, kidney rejection and rheumatoid arthritis.

If you have a replacement therapy with oral oestrogens, it may reduce the effect of Saizen on growth. Therefore your doctor may need to adjust your Saizen dose.

If you are treated with sex hormones, medicines to control epilepsy (anticonvulsants) or cyclosporine (a medicine that weakens the immune system after transplantation), you should tell you doctor as the dose of these medicines may need to be adjusted.

Pregnancy and breast feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
There is currently insufficient evidence from human studies on the safety of growth hormone treatment during pregnancy and breast feeding. Saizen should be discontinued, if pregnancy occurs.

Driving and using machines
No studies on the effects of Saizen on the ability to drive and use machines have been performed. Somatropin-containing products have no influence on the ability to drive and use machines.

Important information about some of the ingredients of Saizen
This medicine contains less than 1 mmol sodium (23 mg) per cartridge, that is to say essentially 'sodium-free'.

3. How to use Saizen

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

Dosage

The dose and frequency of administration of Saizen will be decided by your doctor and will depend on your (or your child's) body weight or body surface area.

It is recommended that Saizen be administered at bedtime.

Children and adolescents:
- Short stature due to a lack of, or insufficient levels of natural growth hormone:
  0.7-1.0 mg/m^2 body surface area each day or 0.025-0.035 mg/kg body weight each day by subcutaneous administration (under the skin).
- Growth failure in girls due to gonadal dysgenesis (Turner syndrome):
  1.4 mg/m^2 body surface area per day or 0.045-0.050 mg/kg body weight each day by subcutaneous administration (under the skin).
  If your daughter is treated for Turner syndrome and she receives non-androgenic anabolic steroids as well, growth response may be enhanced. Ask your doctor or pharmacist if you are not sure about these drugs.
- Growth failure in pre-pubertal children due to chronic renal failure, a condition in which kidneys are damaged:
  1.4 mg/m^2 body surface area, approximately equal to 0.045-0.050 mg/kg body weight each day by subcutaneous administration (under the skin).
- Growth problems in children who were born small:
  1 mg/m^2 body surface area, approximately equal to 0.035 mg/kg body weight each day by subcutaneous administration (under the skin).

Adults:
- Growth hormone deficiency in adults:
  At the start, low doses of 0.15-0.30 mg each day are recommended by subcutaneous injection (under the skin). The dose will be adjusted in stages by your doctor. The recommended final dose of growth hormone rarely exceeds 1.0 mg/day. In general the lowest efficacious dose that works for you should be administered. If you are older or overweight, a lower dose may be necessary.

Method and route of administration

The dose and frequency of administration of Saizen will be decided by your doctor and will depend on your (or your child's) size or body weight. In general Saizen should be administered each day by subcutaneous injection (under the skin).

Important information
For administration of Saizen, please read the following instructions carefully.
When the medicine is injected into the same place every time for a long time, it can cause damage. It is important to keep changing the place where you have your injection. Your doctor or pharmacist can speak to you about which part of the body you should use. Do not use any areas in which you feel lumps, firm knots, depressions, or pain; talk to your doctor or pharmacist about anything you find.
Clean the skin at the injection site with soap and water.

The cartridge containing the solution of Saizen is ready to be used for administration with your cool.click needle-free auto-injectors, easypod auto-injector or aluetta pen injector.
Each Saizen cartridge presentation is colour coded and must be used with the matching colour coded aluetta pen injector to give the correct dose. The cartridge containing 6 mg somatropin (blue) must be used with the aluetta pen injector 6 (blue).

Place all elements needed for the injection of the solution on a clean surface and wash your hands with soap and water.

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

How to perform your daily self-administration of Saizen
For instructions on how to load the cartridge into the cool.click needle-free auto-injectors, easypod auto-injector or aluetta pen injector and inject the solution of Saizen, please carefully read the corresponding instruction manual provided with each injector. Intended users of easypod are primarily children starting from the age of 7 up to adults. Use of the devices by children should always be made under adult's supervision.

Duration of treatment
Your child should stop using this treatment when he or she reaches a satisfactory adult height or his or her bones cannot grow any longer, as assessed by his or her doctor. Treatment with Saizen will be stopped in children with chronic kidney failure at the time of kidney transplant.
In adults a lack of growth hormone is a lifelong condition and it should be treated accordingly by your doctor.

If you use more Saizen than you should
If you inject too much Saizen, you should tell your doctor as it may be necessary to change slightly the dose to make up for this. Injecting too much can lead to changes in blood sugar levels which could mean that you (or your child) will feel shaky and light-headed. If this happens contact your doctor as soon as possible.

If you forget to use Saizen
If you miss a dose, tell your doctor as it may be necessary to slightly change the dose to make up for this.

If you stop taking Saizen
Do not stop taking Saizen without speaking with your doctor.

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

4. Possible side effects

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

Tell your doctor immediately if you experience strong and recurrent headaches associated with feeling sick (nausea), vomiting or sight disturbances. These are symptoms of a side effect called benign intracranial hypertension and it is uncommon.

Side effects may occur with certain frequencies, which are defined as follows:
- very common: may affect more than 1 in 10 people
- common: may affect up to 1 in 10 people
- uncommon: may affect up to 1 in 100 people
- rare: may affect up to 1 in 1,000 people
- very rare: may affect up to 1 in 10,000 people
- not known: frequency cannot be estimated from the available data.

Common side effects:
- Reactions at the injection site such as e.g. redness, itching, swelling, rash, hives, pain, inflammation, bleeding, abnormal collection of blood outside of a blood vessel (haematoma). If this appears to be particularly troublesome, you should discuss this with your doctor.
- Local loss of the fat tissue under the skin, which can be avoided if you change the injection site.
- Carpal tunnel syndrome in adults that is characterised by persistent stinging, burning sensation, pain and/or numbness in the fingers which affect particularly the thumb, index and sometimes also middle and ring finger.
- Fluid retention: peripheral oedema (swelling), muscle pain, numbness and tingling, joint pain, and joint disorders in adult users. These side-effects appear usually early in the treatment, are short-lived and depend on the dose.
- (Isolated) headache.

Uncommon side effects:
- Benign intracranial hypertension (increased intracranial pressure around the brain characterised by headache, nausea, vomiting, double vision and other visual symptoms).
- Carpal tunnel syndrome in children that is characterised by persistent stinging, burning sensation, pain and/or numbness in the fingers which affect particularly the thumb, index and sometimes also middle and ring finger.
- Fluid retention: peripheral oedema (swelling), muscle pain, numbness and tingling, joint pain, and joint disorders in children. These side-effects appear usually early in the treatment, are short-lived and depend on the dose.
- Breast enlargement (one or both sides may be affected).

Very rare side effects:
- Slipped capital femoral epiphysis (a hip problem that starts if the growing end of the thigh bone slips from the ball of the hip joint) and avascular necrosis of the femoral head. If your child shows an unexplained limp and hip or knee pain, please contact your doctor or pharmacist.
- Growth hormone treatment may reduce the levels of thyroid hormone. This can be tested by your doctor and if necessary your doctor will prescribe the adequate treatment.

Side effects with an unknown frequency:
You (or your child) can experience allergic reactions due to the treatment with Saizen.

You (or your child) can experience increased insulin levels (hyperinsulinism) as muscle, fat, and liver cells do not respond properly to insulin during growth hormone treatment (insulin resistance). This condition can result in high blood sugar levels (hyperglycaemia).

Rarely an inflammation of the pancreas has been reported in patients treated with growth hormone.

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.

Very rarely a patient could develop antibodies (type of protein that helps protect the body) to somatropin. These are usually not associated with any side effects and do not usually interfere with growth.

Reporting of side effects:
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

UK:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL -
Dublin 2
Tel:+353 1 6764971
Fax:+353 1 6762517
Website:www.hpra.ie
e-mail:medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Saizen

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

Do not use Saizen after the expiry date which is stated on the cartridge after EXP. The expiry date refers to the last day of that month.

Store the unused Saizen cartridge in a refrigerator (2°C-8°C) in the original package to protect from light. Do not freeze.

After first injection, use within 28 days.

After first injection, the Saizen cartridge, the easypod auto-injector containing the Saizen cartridge or the aluetta pen injector containing the Saizen cartridge has to be stored in a refrigerator (2°C-8°C) for a maximum of 28 days, of which up to 7 days can be outside of a refrigerator at or below 25°C. When stored outside of the refrigerator for up to 7 days, the Saizen cartridge must be returned to the refrigerator and used within 28 days after first injection.

When using the easypod auto-injector or the aluetta pen injector, the cartridge is kept in the device. The cool.click needle-free auto-injector should be stored outside of a refrigerator always separately from the Saizen cartridge. Protect the used cartridge from light.

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 to protect the environment.

6. Contents of the pack and other information

What Saizen contains

The active substance is somatropin (recombinant human growth hormone) 6 mg.
The other ingredients are sucrose, poloxamer 188, phenol, citric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection.

What Saizen looks like and contents of the pack

Saizen 5.83 mg/ml is a clear to slightly opalescent solution for injection in a pre-filled cartridge (type 1 glass) with a plunger stopper (rubber) and a crimp cap (aluminium and rubber), containing a nominal value of 1.03 ml solution (6 mg somatropin). The cartridge containing 6 mg somatropin is marked with a coloured label (blue).

Pack sizes of 1 and 5 cartridges.

Not all pack sizes may be marketed.

Marketing Authorization Holder

UK:
Merck Serono Limited
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX
United Kingdom

IE:
Merck Serono (Ireland) Limited
4045 Kingswood Road
Citywest Business Campus
Dublin 24
Ireland

Manufacturer

Merck Serono SpA, Modugno, Bari, Italy

This medicinal product is authorised in the Member States of the EEA under the following names:

Saizen: Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, Norway, Portugal, Romania, Slovakia, Spain, Sweden, United Kingdom

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