PRODUCT INFORMATION

SAIZEN® Solution for Injection

NAME OF THE MEDICINE

Somatropin (rmc), recombinant human growth hormone

DESCRIPTION

SAIZEN is authentic human growth hormone which is prepared from genetically engineered mammalian cells (recombinant mouse cells - C127) transformed with a bovine papilloma virus vector containing the human growth hormone coding sequence. According to the European Pharmacopoeia, somatropin (rmc) 3 IU equals 1 mg somatropin (rmc) by weight. The dose in mg set out below is based on this equivalence.

SAIZEN solution for injection is presented as a sterile liquid in glass cartridges for multidose use. Each cartridge contains somatropin (rmc) 6 mg/1.03 mL (5.83 mg/mL), 12 mg/1.5 mL (8.00 mg/mL) or 20 mg/2.5 mL (8.00 mg/mL). SAIZEN solution for injection also contains sucrose, poloxamer, phenol and water for injections. Sodium hydroxide and citric acid-anhydrous are used for pH adjustment.

PHARMACOLOGY

Human growth hormone (hGH) is normally secreted at night during sleep and promotes skeletal, visceral and general body growth through the action of somatomedins or insulin-like growth factors (IGFs). Somatropin raises the serum levels of IGF-1. Growth hormone has a role in building and sustaining lean body mass, facilitating the utilisation of fat mass for energy needs, and maintaining bone mineral density. Apart from its effects on growth, hGH has a variety of effects on lipid, protein and carbohydrate metabolism.

Pharmacokinetics

After intramuscular injection of 4 IU somatropin/m² body surface area, $C_{\text{max}}$ (36.9 ± 12.1 ng/mL) was measured at 3 hours ($T_{\text{max}}$). hGH levels returned to pre-injection levels after 12 hours. The $\text{AUC}_{24}$ was 183 ng.h/mL. These pharmacokinetic parameters are similar to those reported in the literature for pituitary derived hGH. After subcutaneous injection, $C_{\text{max}}$ was delayed until 4 - 6 hours post injection. The $\text{AUC}_{24}$ for the two routes of administration were similar.

SAIZEN solution for injection (5.83 mg/mL and 8.00 mg/mL) administered subcutaneously were shown to be bioequivalent to the 8 mg freeze-dried formulation.
CLINICAL TRIALS

Turner Syndrome

An open, randomised, multicentre study (Phase III) was conducted to assess the efficacy and safety of SAIZEN (r-hGH) and of the combination with oxandrolone in 91 growth retarded girls with Turner Syndrome (TS).

The diagnosis of TS was made on the basis of clinical characteristics and verified by karyotype analysis. The inclusion criteria were absence of the 2nd chromosome or chromosome aberrations, chronological age (CA) > 5 years, bone age < 11 years, height at least 2 SD below the mean for CA and post-stimulatory circulating hGH serum levels of > 10 ng/mL.

The girls were randomly allocated to one of two original treatment groups: (1) SAIZEN alone or (2) SAIZEN in combination with the anabolic steroid oxandrolone. Group 1 received 18 IU/m²/week SAIZEN increasing to 24 IU/m²/week after the first year. Group 2 received 18 IU/m²/week SAIZEN and 0.1 mg/kg/day oxandrolone. The oxandrolone dose was reduced to 0.05 mg/kg/day after the first year.

After the second year, the dose of SAIZEN was 24 IU/m²/week for all groups and two further subgroups were formed: (1a) who received 24 IU/m²/week SAIZEN and 0.05 mg/kg/day oxandrolone and (2a) who stopped oxandrolone treatment and received 24 IU/m²/week SAIZEN alone.

Results

This study demonstrated efficacy in Height Velocity (HV), Height SDS - CA, Height, Predicted adult height and Final height, with mean heights in each treatment group ranging from 147.5 to 153.6 cm. The mean (± SD) final height was 150.6 ± 5.5 cm. Fifteen patients developed anti-hGH antibodies on at least 1 occasion. However, as the average height of these patients was 149.3 ± 7.1 cm, the development of antibodies does not appear to have a negative impact on growth.

The use of oxandrolone was not associated with additional final height gain, but was associated with virilising side effects.

Adult Growth Hormone Deficiency (GHD)

A multicentre, randomised, double-blind, placebo-controlled clinical trial was conducted in 115 GHD adults comparing the effects of SAIZEN and placebo on body composition. Patients in the active treatment arm were treated with SAIZEN at an initial dose of 0.005 mg/kg/day for one month which was increased to 0.01 mg/kg/day if tolerated for the remaining five months of the study.

Primary end-points

The primary endpoint was the treatment difference on the change from baseline in lean body mass (LBM) measured by dual energy X-ray absorptiometry (DXA) after 6 months.
Treatment with SAIZEN produced highly significant (p<0.001) increases from baseline in LBM compared to placebo (Table 1).

**Table 1: Lean Body Mass (kg) by DXA**

<table>
<thead>
<tr>
<th></th>
<th>SAIZEN (n=52)</th>
<th>Placebo (n=51)</th>
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<tbody>
<tr>
<td>LBM Baseline (kg)</td>
<td>47.7 ± 11.4</td>
<td>54.0 ± 12.0</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>+ 1.9 ± 2.2</td>
<td>− 0.2 ± 2.3</td>
</tr>
<tr>
<td>Treatment difference</td>
<td>2.1</td>
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<tr>
<td>95% confidence interval</td>
<td>(1.3, 2.9)</td>
<td>&lt;0.001</td>
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Sixty-seven (58%) of the 115 randomised patients were male. The adjusted mean treatment difference on the increase in LBM from baseline was significantly greater in males (2.9 kg) than females (0.8 kg).

Ninety-seven (84%) of the 115 randomised patients had adult onset (AO) GHD. The adjusted mean treatment differences on the increase in LBM from baseline was significantly different in AO GHD (2.1 kg, p<0.001). The difference in childhood onset (CO) GHD (1.0 kg) was not significantly different, however, there were relatively few patients with CO GHD (n=18) on which to base the comparison.

**Secondary end-points**

Treadmill exercise test (Weber protocol): there was a slightly greater increase, albeit not statistically significant, in VO\textsubscript{2max} in the SAIZEN group compared to placebo (SAIZEN: baseline 21.21 ± 7.71 mL/kg/min N = 36, 6 months 25.50 ± 7.78 mL/kg/min N = 26; placebo: baseline 23.36 ± 6.98 mL/kg/min N = 35, 6 months 26.47 ± 8.58 mL/kg/min, N = 31). No statistically significant differences were noted for anaerobic threshold.

Analysis of the treatment difference on the change from baseline in total fat mass (by DXA) revealed: a statistically significant reduction of total fat mass (p<0.0001) in the SAIZEN group compared to placebo (SAIZEN: baseline 27.73 ± 10.72 kg N = 59, 6 months 23.82 ± 9.65 kg N = 52; placebo: baseline 28.90 ± 14.83 kg N= 54, 6 months 29.12 ± 15.33 kg N = 52). Anthropometry demonstrated no statistically significant differences between the treatment groups for skin folds, waist/hip ratio or body weight. The sum of circumferences decreased significantly in the SAIZEN group relative to placebo (p<0.017).

SAIZEN also produced beneficial effects on several bone turnover markers including: bone specific alkaline phosphatase, C-terminal propeptide, osteocalcin and urine deoxypyridinoline and intact parathyroid. The changes in total bone mineral content and body cell mass were not statistically different between the treatment groups.

Perceived well-being: No significant differences were found in Nottingham Health Profile or the General Well-Being Index.
Handgrip strength: No statistically significant differences were found between the treatment groups in the assessments of dominant or non-dominant hand-grip strength.

Mid-thigh cross-sectional MRI: No statistically significant differences were found between the treatment groups in the assessments of percentages of fat, muscle or bone.

Cardiac function: Two-dimensional echocardiography showed statistically significant differences between the treatment groups for ejection fraction percentage (increase in the SAIZEN group, p<0.048; SAIZEN: baseline 54.90 ± 11.21% N = 52, 6 months 60.89 ± 9.47% N = 48; placebo: baseline 54.41 ± 12.91% N = 50, 6 months 57.30 ± 8.61% N = 49) and left ventricular end-systolic volume (decrease in the SAIZEN group, p<0.035; SAIZEN: baseline 35.83 ± 17.61 mL N = 52, 6 months 30.40 ± 15.35 mL N = 49; placebo: baseline 39.04 ± 16.00 mL N = 48, 6 months 37.69 ± 16.64 mL N = 49).

One hundred and eleven patients were treated with SAIZEN for an additional 12 to 36 months in an open label follow up study. During this period, the positive effects on Lean Body Mass and fat mass achieved during initial treatment were maintained.

INDICATIONS

1. Growth failure in children due to human growth hormone deficiency

2. Growth failure in girls with gonadal dysgenesis (Turner Syndrome), confirmed by chromosomal analysis

3. SAIZEN is indicated for replacement therapy in adults with pronounced growth hormone deficiency as diagnosed in 2 different dynamic tests for growth hormone deficiency and defined by peak GH concentrations of less than 2.5 nanogram/mL. Adults 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.

CONTRAINDICATIONS

SAIZEN should not be used for growth promotion in children/patients with closed epiphyses.

SAIZEN should not be used in patients with hypersensitivity to any constituent of the product (see ‘DESCRIPTION’).
SAIZEN is contraindicated where there is evidence of an active intracranial lesion. Intracranial lesions must be inactive for 12 months prior to instituting therapy and SAIZEN should be discontinued if there is any evidence of recurrent activity.

SAIZEN is contraindicated in patients with active neoplasia (either newly diagnosed or current). Any pre-existing neoplasia should be inactive* and any anti-tumour treatment must be completed prior to starting treatment with somatropin. SAIZEN should be discontinued if there is evidence of tumour growth.

Somatropin is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.

SAIZEN should not be initiated to treat patients with acute critical illness due to complications following open heart surgery or abdominal surgery, multiple accident trauma, to patients having acute respiratory failure or patients with similar conditions* (see PRECAUTIONS).

**PRECAUTIONS**

SAIZEN therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of growth hormone deficiency.

When somatropin is administered subcutaneously at the same site over a long period, lipoatrophy may result. This can be avoided by frequent rotation of the injection site.

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. Adult growth hormone deficiency is a lifelong condition. However, caution should be exercised because experience with prolonged treatment in adults is limited. Other hormonal deficiencies found in hypothalamic disease or pituitary disease should be treated with adequate replacement therapy before SAIZEN therapy is instituted.

The effects of *E-coli* derived growth hormone on recovery were studied in two placebo-controlled clinical trials involving 522 adult patients who were critically ill due to complications following open heart or abdominal surgery, multiple accident trauma or who were having acute respiratory failure. Mortality was higher (41.9% vs 19.3%) among growth hormone treated patients (doses 5.3–8 mg/day) than among those receiving placebo. Based on this information, these patients must not be treated with somatropin (see CONTRAINDICATIONS). The safety of continuing growth hormone in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation in patients having acute critical illness should be weighed against the potential risk.

**Hypothyroidism**

The possible appearance of hypothyroidism in the course of therapy with SAIZEN should be corrected with thyroid hormone in order to obtain a satisfactory growth response. Thyroid
assessment, by thyroid hormone level measurements, should be undertaken before starting SAIZEN therapy* and not less frequently than annually.

**Insulin resistance**

Because of its diabetogenic effect, SAIZEN should be used with caution in patients with diabetes mellitus or with a family history of diabetes mellitus. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted.

Growth hormone administration is followed by a transient phase of hypoglycaemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations. Somatropin may induce a state of insulin resistance which can result in hyperinsulinism and in some patients in hyperglycaemia. To detect an insulin resistance, patients should be monitored for evidence of glucose intolerance. Patients with diabetes mellitus or glucose intolerance should be monitored closely during SAIZEN therapy.

**Prader-Willi Syndrome***

While SAIZEN is not indicated for the treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi Syndrome, it should be noted that 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.

**Haematological neoplasms**

An increased incidence of leukaemia in growth hormone deficient children has been observed. A causal relationship to growth hormone therapy has not been established.

**Tumour occurrence and recurrence**

Treatment in growth hormone deficient adults should be attempted only after definitive treatment of pituitary tumour (if present) is completed and all other pituitary hormone deficiencies are corrected as clinically needed.

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

**Slipped capital femoral epiphysis**

Patients receiving growth hormone therapy should be observed for the possible onset of a limp, or complaints of hip or knee pain, as this may indicate the development of slipped capital femoral epiphyses.
**Idiopathic intracranial hypertension**

Fundoscopic examination should be performed routinely before initiating treatment with SAIZEN to exclude pre-existent papilloedema and repeated if there is any clinical suspicion.* In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of idiopathic intracranial hypertension should be considered and if appropriate, the growth hormone treatment should be discontinued.

At present, there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

**Antibodies**

As with all somatropin-containing products, a small percentage of patients may develop antibodies to SAIZEN. 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.

**Effects on fertility**

In *E-coli* derived growth hormone studies, reproduction was inhibited in male and female rats at doses of 3 IU/kg/day (1 mg/kg/day) or more, with reduced copulation and conception rates, lengthened or absent oestrus cycles, and at 10 IU/kg/day (3.3 mg/kg/day), a lack of responsiveness of females to males, and slight reductions in sperm motility and survival. Rat reproduction was unaffected by (0.3 mg/kg/day) somatropin, which resulted in a systemic exposure (based on body surface area) of approximately twice that anticipated at the maximum clinical dose.

In reproduction studies using recombinant mouse cell derived somatropin, no effects on female fertility were observed in rats treated with somatropin at subcutaneous doses of up to 10 IU/kg/day (equivalent to 20 mg/m²/day, about 14 times the maximum clinical dose on a body surface area basis).

**Use in pregnancy (Category B1)**

Somatropin was not teratogenic in rats or rabbits at respective doses of up to 14 and 22 times the maximum recommended clinical dose (4.3 IU or 1.4 mg/m²/day), based on body surface area. In rats, somatropin administered from late gestation to weaning, at 14 times the clinical dose based on body surface area, was associated with increased body weight of pups at birth and postnatally. There are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

**Use in lactation**

There have been no clinical studies conducted with somatropin in breastfeeding women. It is not known whether somatropin is excreted in human milk. Therefore, caution should be exercised when SAIZEN is administered to breastfeeding women.
Following subcutaneous administration of radiolabelled somatropin to lactating rats, radioactivity was transferred to milk reaching four times the concentration found in maternal plasma. However, absorption of the intact protein in the gastrointestinal tract of the infant is extremely unlikely.

**Use in the elderly**

Experience in patients over 60 years is limited.

**Carcinogenicity**

Associations between elevated serum IGF-1 concentrations and risk of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

**Genotoxicity**

There was no evidence of genotoxicity in assays for gene mutation in bacteria, chromosomal damage in human lymphocytes and rat bone marrow cells, gene conversions in yeast or unscheduled DNA synthesis in human carcinoma cells.

**INTERACTIONS WITH OTHER MEDICINES**

Concomitant corticosteroid therapy may inhibit the response to SAIZEN. No incompatibilities of SAIZEN with other pharmaceutical preparations are presently known.

Published *in vitro* data indicate that growth hormone may be an inducer of cytochrome P450 3A4. The clinical significance of this observation is unknown. However, when SAIZEN is administered in combination with drugs known to be metabolised by CYP450 3A4 hepatic enzymes, it is advisable to monitor clinical effectiveness of such drugs.

**ADVERSE EFFECTS**

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

- Very common: $\geq 1/10$
- Common: $\geq 1/100$ to $< 1/10$
- Uncommon: $\geq 1/1,000$ to $< 1/100$
- Rare: $\geq 1/10,000$ to $< 1/1,000$
- Very rare: $< 1/10,000$

**Application site disorders**

- Common: Injection site reactions (pain, numbness, redness, swelling)
- Localised lipoatrophy, which can be avoided by varying the site of injection
Body as a whole – General disorders


Central Nervous System

Uncommon: Idiopathic intracranial hypertension (benign intracranial hypertension)

Endocrine disorders

Very rare: Hypothyroidism

Musculo-skeletal disorders

Very rare: Slipped capital femoral epiphysis (epiphysiolysis capitis femoris)

Metabolism disorders

Insulin resistance can result in hyperinsulinism and in rare cases in hyperglycaemia.

Hypothyroidism has been reported in a small number of patients during SAIZEN therapy. It should be noted, however, that hypothyroidism can occur in untreated Turner Syndrome patients.

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.

As with all somatropin containing products, a small percentage of patients may develop antibodies to SAIZEN. 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.

Common adverse effects reported in SAIZEN trials that were not considered to be treatment-related included: upper respiratory tract infection, fever, headache, pharyngitis, otitis media, coughing, vomiting, dyspepsia.

Glucose intolerance was not seen during clinical studies but a number of subjects had relatively high insulin levels during oral glucose tolerance tests.
DOSAGE AND ADMINISTRATION

Recommended Dosage

Treatment should be discontinued when a satisfactory adult height has been reached or when epiphyses are closed.

The maximum recommended daily dose should not be exceeded.*

1. Treatment of growth failure due to growth hormone deficiency in children

The recommended weekly dose is as follows:

- 0.2 mg/kg body weight
- 4 mg/m² BSA (Body Surface Area)

The weekly dose may be divided as shown below and is expressed per injection:

<table>
<thead>
<tr>
<th>Doses</th>
<th>0.07 mg/kg body weight</th>
<th>1.3 mg/m² BSA</th>
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<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.03 mg/kg body weight</td>
<td>0.7 mg/m² BSA</td>
</tr>
<tr>
<td>7</td>
<td>0.03 mg/kg body weight</td>
<td>0.6 mg/m² BSA</td>
</tr>
</tbody>
</table>

2. Treatment of growth failure in girls with gonadal dysgenesis (Turner Syndrome)

The recommended daily dose is:

- 0.045 – 0.05 mg/kg body weight
- 1.4 mg/m² BSA

3. Treatment of Growth Hormone Deficiency in adults

At the start of SAIZEN therapy, low doses of 0.15 – 0.3 mg are recommended, given as a daily subcutaneous injection. The dose should be titrated carefully guided by IGF-1 age-adjusted normal values and on the basis of clinical effect and adverse events. The recommended final SAIZEN 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.

Administration

For drug preparations intended for self-administration by subcutaneous injection, patients should be thoroughly instructed in the correct administration procedures. This is especially important if injection devices are used in combination with multidose drug preparations. Before using the injection devices, patients should be thoroughly trained to ensure that they are competent in the operation of the device. Periodic monitoring/supervision are also advisable.
SAIZEN is administered by subcutaneous injection, preferably in the evening. The injection site should be alternated to prevent lipoatrophy.

SAIZEN solution for injection must be administered with the dedicated autoinjector device provided separately. For administration, refer to the instructions provided with the device. The solution should not be administered if it contains particles or is not clear.

**OVERDOSAGE**

Overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Moreover, somatropin overdose is likely to cause fluid retention. Long-term overdosage could result in signs and symptoms of acromegaly.

Contact the Poisons Information Centre on 131 126 for advice on the management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

SAIZEN solution for injection is supplied in packs of 1 or 5§ glass cartridges for multidose use in one patient only. Each cartridge contains somatropin (rmc) 6 mg/1.03 mL (5.83 mg/mL), 12 mg/1.5 mL (8.00 mg/mL) or 20 mg/2.5 mL (8.00 mg/mL).

SAIZEN solution for injection should be stored at 2°C to 8°C (Refrigerate. Do not freeze) in the original package in order to protect from light.

SAIZEN solution for injection should be used with the dedicated autoinjector device provided separately. After the first injection, the contents of the cartridge should be used within 28 days and stored at 2°C to 8°C (Refrigerate. Do not freeze).

§ Not currently marketed.

**NAME AND ADDRESS OF THE SPONSOR**

Merck Serono Australia Pty Ltd
3-4/25 Frenchs Forest Rd
Frenchs Forest NSW 2086

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 (Prescription Only Medicine)

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):**
22 August 2011

**Date of most recent amendment: 15 August 2012**

* Registered Trade Mark

* Please note changes in Product Information.