

NEW ZEALAND DATA SHEET

Name of Medicine

SAIZEN®

Somatropin (rmc*) recombinant human growth hormone 1.33, 3, 8 and 8 mg click.easy

*recombinant mouse cell

Presentation

SAIZEN is a freeze-dried preparation intended for subcutaneous injection after reconstitution with solvent. 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. Four different presentations of SAIZEN are available:

SAIZEN 1.33

One vial of freeze-dried product contains 1.33 mg somatropin as active constituent and mannitol, sodium phosphates, sodium chloride, as excipients. One ampoule of solvent contains 1 mL of isotonic, sterile and pyrogen-free saline solution (0.9% w/v sodium chloride).

SAIZEN 3

One vial of freeze-dried product contains 3 mg somatropin as active constituent and mannitol, sodium phosphates, as excipients. One vial of solvent contains 5 mL of isotonic, sterile and pyrogen-free bacteriostatic saline solution (0.9% w/v sodium chloride and 0.9% w/v benzyl alcohol). This product is intended for multidose use.

SAIZEN 8

One vial of freeze-dried product contains 8 mg somatropin as active constituent and sucrose, phosphoric acid, sodium hydroxide, as excipients. One vial of solvent contains 5 mL 0.3% (w/v) meta-cresol in Water for Injections. This product is intended for multidose use.

SAIZEN 8 mg click.easy

One vial of freeze-dried product contains 8 mg somatropin as active constituent and sucrose, phosphoric acid, sodium hydroxide, as excipients. One cartridge of solvent contains 1.37 mL 0.3% (w/v) meta-cresol in Water for Injections.

(click.easy® is a pre-assembled reconstitution device which comprises; a vial of freeze-dried powder, a cartridge of solvent and a sterile transfer cannula).

Uses

Actions

SAIZEN is authentic human growth hormone (somatropin), 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. 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. 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 (rmc)/m² body surface, C_{max} (36.9+12.1ng/mL) was measured at 3 hours (T_{max}). hGH levels returned to pre-injection levels after 12 hours. The AUC₂₄ was 183ng.h/mL. These pharmacokinetic parameters are similar to those reported in the literature for pituitary derived hGH. After subcutaneous injection C_{max} was delayed until 4 - 6 hours post injection. The AUC₂₄ for the two routes of administration were similar.

Indications

SAIZEN is indicated for:

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.

Dosage and administration

In general,

- For drug preparations intended for **self-administration by subcutaneous injection**, patients should be thoroughly instructed in the correct administration procedures – including methods of preparation, reconstitution and injection techniques.
- 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 is also advisable.

SAIZEN is administered by subcutaneous injection, preferably in the evening.

The injection site should be alternated to prevent lipoatrophy.

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

1. Treatment of growth failure due to growth hormone deficiency

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:

3 single doses	0.07 mg/kg body weight 1.3 mg/ m ² BSA
6 single doses	0.03 mg/kg bodyweight 0.7mg/m ² BSA
7 single doses	0.03 mg/kg body weight 0.6mg/ m ² BSA

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/m ² BSA

3. Treatment of 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 titrated carefully guided by IGF-1 age-adjusted normal values and on the basis of clinical effect and adverse events. The recommended final GH dose seldom exceeds 1.0 mg/day. In general the lowest efficacious dose should be administered. In older or overweight patients, lower doses may be necessary.

Reconstitution

The freeze-dried material should be reconstituted with the solvent provided using a gentle swirling motion. Shaking should be avoided. The resulting solution should be without particulate matter. If the solution contains particles, the contents must not be injected.

SAIZEN 1.33

Reconstitute the freeze-dried material containing 1.33 mg somatropin in the vial with one ampoule of 1 mL of solvent (0.9% sodium chloride). The calculated dose should be withdrawn for injection and the remaining contents should be discarded.

Reconstituted SAIZEN 1.33 mg solution must be used immediately, if not it must be stored at 2-8°C (Refrigerate. Do not freeze) and used within 24 hours. The solvent used to reconstitute SAIZEN 1.33 mg contains no antimicrobial agent. Use once and discard any residue.

SAIZEN 3

Reconstitute the freeze-dried material containing 3 mg somatropin with bacteriostatic sodium chloride solution to a concentration of up to 3.33 mg/mL. Following reconstitution, the vial should be swirled with a gentle rotary motion until the contents are completely dissolved. Do not shake.

Reconstituted SAIZEN 3 solution must be stored at 2-8°C and used within 21 days.

SAIZEN 8

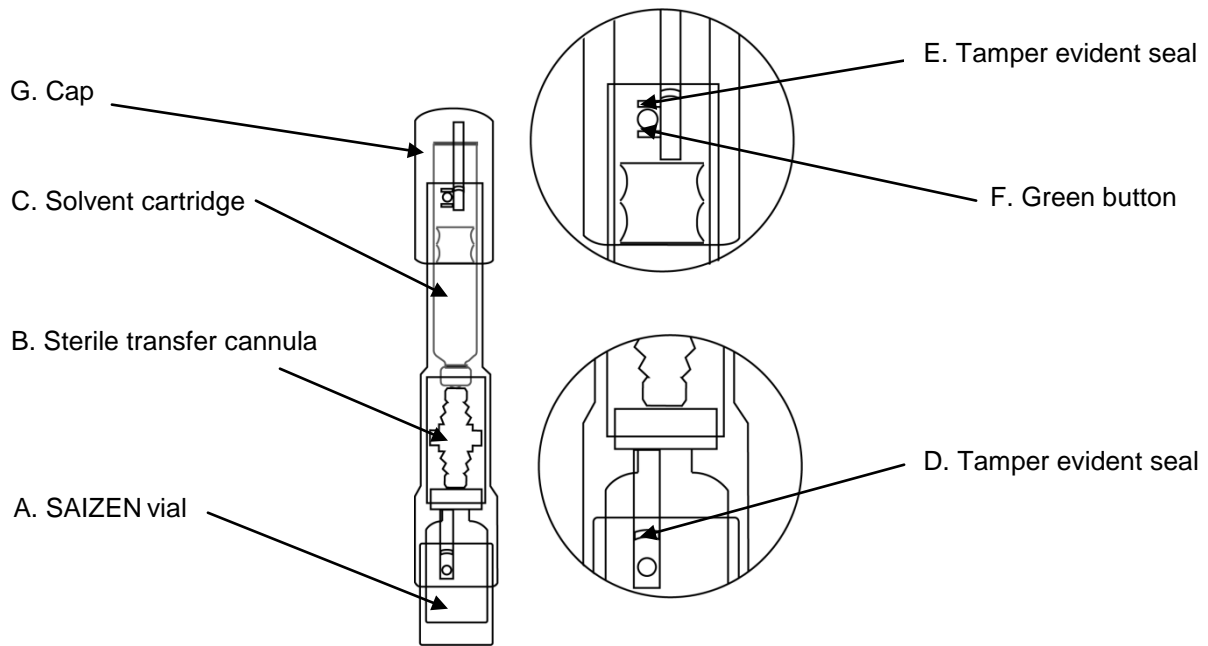
Use with syringe - Reconstitute the freeze-dried material containing 8 mg somatropin in the vial using 2.7 mL of the solvent supplied. Following reconstitution, the vial should be swirled with a gentle rotary motion until the contents are completely dissolved. Do not shake. The final solution contains approximately 3.33 mg/mL somatropin.

Reconstituted SAIZEN 8 solution must be stored at 2-8°C and used within 21 days.

SAIZEN 8 mg click.easy

Instructions for use of SAIZEN 8 mg click.easy

- Make sure the click.easy reconstitution device (see diagram below) is complete by checking that the SAIZEN vial (A), the sterile transfer cannula (B) and the solvent cartridge (C) are present.
- Check that the tamper evident seals (D) and (E) are not broken. Check that the green button (F) is not engaged in the vertical opening. If the tamper evident seals are broken or the green button is engaged in the vertical opening, return it to your pharmacist or doctor.
- Wash your hands with soap and water.



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

- 1) Stand the click.easy vertically on a flat surface with the vial (A) at the bottom and the cap (G) facing upward.
- 2) Push the cap down until it will go no further (Note: the tamper evident seal on the click.easy housing (D) is now broken).
- 3) Turn the cap clockwise until the green button (F) is visible in the vertical opening.
- 4) Continue pushing the cap down very slowly, until it will go no further, to transfer the solvent from the cartridge (C) into the vial (Note: the tamper evident seal (E) on the cap is now broken). It is important to push slowly to prevent foam to appear in the vial. Check that all the solvent has been transferred into the vial.
- 5) Dissolve the powder with the solvent by gently swirling the click.easy (Note: Avoid vigorous shaking to prevent creation of foam). Let the solution stand until the powder is completely dissolved.
- 6) Turn the click.easy upside down (vial on top). Push the cap up until it will go no further and subsequently pull the cap slowly downwards until the solution is completely drawn back into the cartridge.

Check that no more than one or two drops of solution remain in the vial.

If there are more than one or two drops of solution remaining in the vial, slowly push the cap up until some of the solution is back in the vial and gently tap the click.easy. Then draw the solution again slowly again back into the cartridge.

Remove any excess air that has been drawn into the cartridge by slowly pushing the cap upwards

(Note: Avoid pulling the cap downwards too fast, as this will draw air into the cartridge).

- 7) Keeping the click.easy in this position (vial on the top) unscrew the cap and remove it. Do not pull the cap as this will remove the cartridge stopper. Still keeping the same position (vial on top) remove the cartridge containing the reconstituted solution for injection from the click.easy.

- 8) Carefully peel off the outer label using the tab provided. Write the reconstitution date on the transparent inner label on the cartridge.

Discard the click.easy safely in accordance with your local requirements.

The cartridge containing the reconstituted solution of SAIZEN is now ready to be used for administration

The reconstituted solution is not stable at room temperature and must be stored at 2° to 8°C (Refrigerate. Do not freeze). Protect from light and use within 28 days.

Contraindications

SAIZEN should not be used for 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. Any anti-tumour activity 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 or to patients having acute respiratory failure (see PRECAUTIONS).

Warnings and 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. Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. 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 not less frequently than annually. When somatropin (rmc) 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.

The solvent used to reconstitute SAIZEN 3 contains benzyl alcohol. Benzyl alcohol as a preservative in bacteriostatic sodium chloride solution for injection may cause toxic reactions and allergic reactions in infants and children up to 3 years old and must not be given to premature babies or neonates. SAIZEN 3 may be reconstituted with sterile sodium chloride solution or sterile Water for Injections when administering to children under 3 years of age.

In this case, the reconstituted SAIZEN 3 must be stored at 2° to 8°C (Refrigerate. Do not freeze). Protect from light and used within 24 hours.

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 hypoglycemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations. Somatropin may induce a state of insulin resistance which can result in hyperinsulinism and in some patients in hyperglycemia. To detect 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.

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

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 should be examined frequently for progression or recurrence of the underlying disease process.

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.

In the case of myalgia or disproportionate pain at the injection site, myositis should be considered as myositis is a very rare adverse event that may be related to the preservative meta-cresol. If confirmed, an alternative diluent should be used. If an unpreserved diluent is used, the reconstituted product (if not used immediately) must be stored at 2° to 8°C (Refrigerate. Do not freeze). Protect from light and used within 24 hours.

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.

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. 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.

Experience in patients over 60 years is limited.

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 somatropin therapy is instituted.

A small percentage of patients may develop antibodies to SAIZEN. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy. (Refer to 'Adverse Effects')

Carcinogenicity, mutagenicity, impairment of fertility

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. There were 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.

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 SC 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 and Lactation

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 drug 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.

Adverse effects

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

Very Common	$\geq 1/10$
Common	$> 1/100 - < 1/10$
Uncommon	$> 1/1000 - < 1/100$
Rare	$> 1/10000 - < 1/1000$
Very rare	$\leq 1/10000$

Application site disorders

Common

Injection site reactions (pain numbness, redness, swelling)
Localized lipoatrophy, which can be avoided by varying the site of injection

Body as a whole – General disorders

Common (in adults) Uncommon (in children)

Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paresthesia.

CNS

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 hyperglycemia.

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.

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

Interactions

Interactions with other Drugs

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 somatropin 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.

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.

Please advise patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much SAIZEN.

Pharmaceutical precautions

Storage and Shelf life

SAIZEN 1.33 and **SAIZEN 3** should be stored at 2-8°C (Refrigerate. Do not freeze) and protected from light. The shelf life of these products is 2 years.

SAIZEN 8 and **SAIZEN 8 mg click.easy** should be stored below 25°C and protected from light.

The shelf life of the product is 3 years.

Keep out of reach of children. Do not use after the expiry date.

Medicine classification

Prescription Medicine

Package quantities

SAIZEN 1.33

As single cartons or boxes of 10:

One vial of 1.33 mg freeze-dried somatropin accompanied by one ampoule of 1 mL of 0.9% w/v sodium chloride solution.

SAIZEN 3

Either one or ten vials of freeze-dried material containing 3 mg somatropin (rmc) and a corresponding number of vials containing bacteriostatic sodium chloride injection as solvent.

SAIZEN 8

Use with syringe,

Cartons of one or five vials of 8 mg freeze-dried somatropin accompanied by one or five vials of 0.3% w/v meta-cresol in Water for Injections as solvent.

SAIZEN 8 mg click.easy

Either one or five vials of freeze-dried material containing 8 mg somatropin (rmc) and a corresponding number of cartridges of solvent (containing 0.3% metacresol in Water for Injections) pre-assembled in a corresponding number of reconstitution device (click.easy).

Further information

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 & 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+5.5cm. 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

A multicenter, 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. 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

	SAIZEN (n=52)	Placebo (n=51)
LBM Baseline (kg) (mean) SD: 12.325 ± 2.17 kg	47.7	54.0
Change from baseline at 6 months (LBM, kg) (mean) SD: 2.21± 2.17 kg	+1.9	-0.2
Treatment difference (LBM, kg)		

(mean)	2.1
95% confidence interval	(1.3, 2.9)
p-value	<0.001

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_2 max in the r-hGH group compared to placebo (r-hGH: 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 r-hGH group compared to placebo (r-hGH: 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 between-group differences for skinfolds, waist/hip ratio or body weight. The sum of circumferences decreased significantly in the r-hGH 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 other 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 r-hGH group, $p < 0.048$; r-hGH: baseline $54.90 \pm 11.21\%$, $N = 52$, 6 months $60.89 \pm 9.47\%$, $N = 48$; placebo: baseline $54.41 \pm 12.91\%$, $N = 50$, 6 months $57.30 \pm 8.61\%$, $N = 49$) and left ventricular end-systolic volume (decrease in the r-hGH group, $p < 0.035$; r-hGH: 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.

Name and address

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland

Ph: (09) 918 5100
Fax: (09) 9185101

DATE OF PREPARATION

19 September 2011