**AUSTRALIAN PRODUCT INFORMATION – SAIZEN® (somatropin) solution for injection**

## 1. NAME OF THE MEDICINE

Somatropin (rmc), recombinant human growth hormone

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**SAIZEN solution for injection**

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 injection. Sodium hydroxide and citric acid are used for pH adjustment.

## 3. PHARMACEUTICAL FORM

**SAIZEN solution for injection**
SAIZEN solution for injection is presented as a sterile liquid (opalescent white to off-white solution, practically free from visible particles) in glass cartridges for multidose use.

## 4. CLINICAL PARTICULARS
### 4.1. THERAPEUTIC INDICATIONS

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

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

III. Growth disturbance (growth retardation) in pre-pubertal children due to chronic renal insufficiency (CRI)

IV. Growth disturbance (current height standard deviation score (H SDS) <-2.5 and parental adjusted H SDS <-1) in short children born small for gestational age (SGA) with a birth weight and/or length below -2 standard deviations (SD), who failed to show catch-up growth (height velocity standard deviation score (HV SDS) <0 during the last year) by four years of age or later

V. 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.

## 4.2. DOSE AND METHOD OF ADMINISTRATION

### 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.

### I. 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/$m^2$ 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<br>1.3 mg/$m^2$ BSA |
| 6 single doses | 0.03 mg/kg body weight<br>0.7 mg/$m^2$ BSA |
| 7 single doses | 0.03 mg/kg body weight<br>0.6 mg/$m^2$ BSA |

### II. 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

### III. Treatment of growth disturbance in children with chronic renal insufficiency

The recommended daily dose is:
0.045 – 0.05 mg/kg body weight
1.4 mg/$m^2$ BSA

For Healthcare Professionals, please also refer to the Section 100 Growth Hormone Program on the PBS website.

### IV. Treatment of growth disturbance in short children born small for gestational age

The recommended starting daily dose is:
0.035 mg/kg body weight

1 mg/$m^2$ BSA

The dose may be increased to a maximum recommended dose of 0.067 mg/kg/day (2 mg/$m^2$/day) based on clinical judgement.

Treatment is usually recommended until final height is reached. Treatment should be discontinued after the first year if HV SDS is below +1. Treatment should be discontinued when final height is reached (defined as height velocity <2 cm/year) and if bone age is >14 years (girls) or >16 years (boys), corresponding to closure of the epiphyseal growth plates.

**V. 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. With women showing an increasing IGF-1 sensitivity over time, dose adjustment may be required for women, especially for those on oral estrogen replacement. In older or overweight patients, lower doses may be necessary.

**Method of Administration**

For medicine 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 medicine 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 localised lipoatrophy.

**SAIZEN solution for injection**

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

## 4.3. 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 Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION).

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 recurrent). 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.

SAIZEN 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In children with chronic renal disease, treatment with somatropin must be discontinued at the time of renal transplantation.

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, localised lipoatrophy may result. This can be avoided by frequent rotation of the injection site.

### 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. 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.

### Critically ill patients

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 Section 4.3 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 somatropin can decrease insulin sensitivity, patients treated with growth hormone should be monitored for evidence of glucose intolerance. 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.

**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-1 level before start of treatment and twice a year thereafter. If on repeated measurements IGF-1 levels exceed +2 SD compared to references for age and pubertal status, the IGF-1/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.

**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**

There are only limited data available in regard to the risk of tumour development under treatment with growth hormone. Therefore, patients treated with growth hormone should be carefully monitored.

In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with growth hormones.

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.

**Pancreatitis**

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. Signs of scoliosis should be monitored during treatment.

**Slipped capital femoral epiphysis and osteonecrosis of the femoral head**

Patients with endocrine disorders, including growth hormone deficiency (GHD), as well as those with rapid growth, are at increased risk of epiphysiolysis of the hip compared to the general population. Cases of slipped capital femoral epiphysis or osteonecrosis of the femoral head (including Legg-Calve-Perthes syndrome) have been reported in patients treated with somatropin. Growth spurts may increase the risk of joint-related problems, the hip joint being under particular strain during the prepubertal growth spurt. 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 epiphysis.

Patients with growth retardation due to chronic renal insufficiency should be regularly examined and monitored for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may occur in children with advanced renal osteodystrophy and it is uncertain whether these complications are affected by

growth hormone therapy. Assessment of the hip should be obtained prior to initiating therapy and at regular intervals upon discretion of the physician.

**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 by fundoscopy, 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 (also see Section 4.8 ADVERSE EFFECTS).

**Chronic renal insufficiency (CRI)**

In children with chronic renal insufficiency, 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 or upon physician discretion (for example not less than 6 months in the older children) before institution of therapy. Conservative treatment for renal insufficiency should have been established and should be maintained during treatment. Treatment should be discontinued at the time of renal transplantation.

**Use in renal impairment**

Somatropin clearance is known to be reduced in patients with renal impairment. However, based on clinical data there is no need for dosage adjustment.

**Use in 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.

**Use in the elderly**

Experience in patients over 60 years is limited.

**Paediatric use**

This medicine is indicated for use in paediatric populations (see Sections 4.1 THERAPEUTIC INDICATIONS, 4.2 DOSE AND METHOS OF ADMINISTRATION, 4.3 CONTRAINDICATIONS and 5.1 PHARMACOLOGICAL PROPERTIES).

**Effects on laboratory tests**

No data available

## 4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant corticosteroid therapy may inhibit the response to SAIZEN. If glucocorticoid replacement is required, the dose of somatropin should be carefully adjusted.
In addition, initiation of growth hormone replacement may unmask secondary adrenal insufficiency in some patients by reducing the activity of 11β-hydroxysteroid dehydrogenase, type 1 (11β-HSD1), an enzyme converting inactive cortisone to cortisol. Initiation of somatropin in patients receiving glucocorticoid replacement therapy may lead to manifestation of cortisol deficiency. Adjustment of glucocorticoid dose may be required.

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, patients receiving oral estrogen replacement may require dosage adjustment of somatropin. If a woman taking somatropin begins oral estrogen therapy, the dose of somatropin may need to be adjusted to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral estrogen therapy, the dose of somatropin may need to be adjusted to avoid excess of growth hormone and/or side effects.

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 medicines known to be metabolised by CYP450 3A4 hepatic enzymes, it is advisable to monitor clinical effectiveness of such medicines.

## 4.6. FERTILITY, PREGNANCY AND LACTATION

**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/m$^2$/day, about 14 times the maximum clinical dose on a body surface area basis).

**Use in pregnancy (Category B1)**

There are no adequate and well-controlled studies in pregnant women. 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/$m^2$/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. 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.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to its pharmacological profile somatropin is unlikely to impair the patient's ability to drive or to operate machinery.

## 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Clinical trial experience**

***SGA indication***

Based on published literature and company sponsored studies, the most frequently reported adverse events were headache, arthralgia, bronchitis, pyrexia, nasopharyngitis, upper respiratory tract infection, asthenia, abdominal pain, gastroenteritis, injection site pain, ear infection, pain in extremity, tonsilitis, rhinitis, varicella. Many of these events reflect commonly observed childhood infections or accidental injuries.

In a company sponsored study IMP 20184 (continuation of studies GF 4001 and GF 6283), Table 1 summarises the adverse events that occurred in at least 5% of patients treated with Saizen compared to no treatment. The dose used in IMP 20184, as well as the previous studies (GF 4001 and GF 6283) was 0.067 mg/kg/day.

**Table 1 Most common adverse events experienced by at least 5% in either treated or non-treated subjects within Preferred Term – by System Organ Class and Preferred term – Safety Population (Study IMP20184)**

| System Organ Class<br>Preferred Term | Not Treated Subjects (n=32) | | Treated Subjects (n=59) | |
|---|---|---|---|---|
| | Subjects<br>n (%) | Events<br>n (%) | Subjects<br>n (%) | Events<br>n (%) |
| Patients with events and total events | 16 (50.0) | 45 (100) | 52 (88.1) | 263 (100) |
| Infections and infestations | 8 (25.0) | 22 (48.9) | 30 (50.8) | 80 (30.4) |
| Pharyngitis | 5 (15.6) | 6 (13.3) | 9 (15.3) | 14 (5.3) |
| Bronchitis | 3 (9.4) | 6 (13.3) | 8 (13.6) | 11 (4.2) |
| Gastroenteritis | 3 (9.4) | 3 (6.7) | 7 (11.9) | 8 (3.0) |
| Nasopharyngitis | | | 6 (10.2) | 11 (4.2) |
| Influenza | | | 6 (10.2) | 8 (3.0) |
| Ear infection | 2 (6.3) | 3 (6.7) | 4 (6.8) | 4 (1.5) |
| Rhinitis | 1 (3.1) | 1 (2.2) | 4 (6.8) | 4 (1.5) |
| Musculoskeletal and connective tissue disorders | | | 19 (32.2) | 30 (11.4) |
| Arthralgia | | | 7 (11.9) | 8 (3.0) |
| Back pain | | | 4 (6.8) | 7 (2.7) |
| Skin and subcutaneous tissue disorders | 2 (6.3) | 4 (8.9) | 16 (27.1) | 21 (8.0) |
| Acne | 1 (3.1) | 2 (4.4) | 6 (10.2) | 7 (2.7) |
| Eczema | 1 (3.1) | 2 (4.4) | 4 (6.8) | 4 (1.5) |
| Injury, poisoning and procedural complications | 3 (9.4) | 3 (6.7) | 14 (23.7) | 17 (6.5) |
| Joint sprain | | | 4 (6.8) | 4 (1.5) |
| Nervous system disorders | 2 (6.3) | 3 (6.7) | 13 (22.0) | 18 (6.8) |
| Headache | 1 (3.1) | 2 (4.4) | 10 (6.9) | 14 (5.3) |
| Reproductive system and breast disorders | 3 (9.4) | 3 (6.7) | 9 (15.3) | 10 (3.8) |
| Gynaecomastia | | | 3 (5.1) | 3 (1.1) |
| Gastrointestinal disorders | 1 (3.1) | 1 (2.2) | 10 (16.9) | 13 (4.9) |
| Abdominal pain | | | 4 (6.8) | 4 (1.5) |
| General disorders and administration site conditions | 2 (6.3) | 2 (4.4) | 6 (10.2) | 6 (2.3) |
| Pyrexia | 1 (3.1) | 1 (2.2) | 3 (5.1) | 3 (1.1) |
| Eye disorders | 1 (3.1) | 1 (2.2) | 5 (8.5) | 11 (4.2) |
| Conjunctivitis allergic | | | 3 (5.1) | 7 (2.7) |
| Immune system disorders | | | 4 (6.8) | 6 (2.3) |
| Seasonal allergy | | | 3 (5.1) | 5 (1.9) |
| Ear and labyrinth disorders | | | 4 (6.8) | 5 (1.9) |

| | | | | |
|---|---|---|---|---|
| Hypoacusis | | | 3 (5.1) | 3 (1.1) |

***Adverse events in other indications***

Common adverse events 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.

## Adverse reactions or effects

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

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

**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**

Common (in adults) Uncommon (in children): Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paraesthesia

**Nervous system disorders**

Common: Headache, carpal tunnel syndrome (in adults)

Uncommon: Idiopathic intracranial hypertension (benign intracranial hypertension), carpal tunnel syndrome (in children)

**Endocrine disorders**

Very rare: Hypothyroidism

**Gastrointestinal disorders**

Frequency not known: Pancreatitis

**Immune system disorders**

Frequency not known: Localised and general hypersensitivity reactions

**Reproductive system and breast disorders**

Uncommon: Gynaecomastia

**Musculo-skeletal disorders**

| | |
|---|---|
| Frequency not known: | Avascular necrosis of the femoral head (incl. Legg-Calve-Perthes disease), Slipped capital femoral epiphysis (epiphysiolysis capitis femoris) |

**Metabolism disorders**

Frequency not known: Hyperglycaemia, hyperinsulinism, insulin resistance

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 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 adverse 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.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9. OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia) or 0800 764 766 (New Zealand).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

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.

**Clinical trials**

**Inadequate Endogenous Growth Hormone Secretion in Children**

Efficacy and safety of SAIZEN have been studied in five pivotal studies using pre-treatment growth measurements compared with treatment growth measured as a method of control.

The effectiveness of growth hormone treatment on growth was assessed primarily by changes in Height Velocity Standard Deviation Score (HV SDS) and Height SDS (H SDS) after at least 24 months of treatment. r-hGH was administered subcutaneously in all of the studies. Patients were randomised in two groups: Group 1 (n=203; 178 naïve, 25 non-naïve) who received r-hGH 0.6 IU/kg body weight/week (0.2 mg/kg/week) via subcutaneous injections three times a week (higher dose, lower frequency); and Group 2 (n=101; 47 naïve, 54 non-naïve) who received r-hGH 0.45 IU/kg body weight/week (0.15 mg/kg/week) seven times a week (lower dose, higher frequency).

Of the 304 prepubertal children included, 225 were previously untreated (treatment-naïve children) and 79 had been switched to r-hGH (SAIZEN) from pituitary-derived hGH after interruption of therapy for at least 6 months. For both naïve and transfer patients in both groups, there was a significant increase in HV, HV SDS and H SDS, at 1 and 2 years, as shown in Table 2.

**Table 2: HV, HV SDS and H SDS Prior to and during the 1st and 2nd Years of Treatment (a) Naïve and (b) Transfer Patients who Completed 2 Years of Therapy**

| | (a) Naïve Patients (24-month treatment only) | | | | | |
|---|---|---|---|---|---|---|
| | Group 1* (n=87) | | | Group 2* (n=22) | | |
| | Baseline | 1st year | 2nd year | Baseline | 1st year | 2nd year |
| HV (cm/year) | 3.5 ± 1.2 | 8.6 ± 2.0 | 6.6 ± 1.4 | 3.4 ± 1.1 | 11.0 ± 2.7 | 7.1 ± 1.2 |
| HV SDS | -2.8 ± 1.6 | +4.2 ± 2.2 | +2.0 ± 1.5 | -3.3 ± 1.5 | +5.7 ± 2.0 | +1.8 ± 1.7 |
| H SDS | -4.2 ± 1.3 | -3.4 ± 1.1 | -3.0 ± 1.2 | -4.4 ± 1.0 | -3.1 ± 0.8 | -2.7 ± 0.9 |
| | (b) Transfer Patients (24-month treatment only) | | | | | |
| | Group 1* (n=14) | | | Group 2* (n=32) | | |
| | Baseline | 1st year | 2nd year | Baseline | 1st year | 2nd year |
| HV (cm/year) | 3.2 ± 1.1 | 7.2 ± 2.9 | 5.0 ± 1.6 | 2.3 ± 1.3 | 10.0 ± 1.9 | 6.8 ± 1.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HV SDS | -2.2 ± 1.7 | +4.2 ± 4.3 | +1.6 ± 2.4 | -3.3 ± 2.4 | +7.8 ± 2.5 | +3.9 ± 2.6 |
| H SDS | -3.9 ± 1.5 | -3.3 ± 1.6 | -3.1 ± 1.5 | -4.4 ± 1.5 | -3.3 ± 1.4 | -2.8 ± 1.4 |

*Group 1: 3 injections/week; Group 2: 7 injections/week

Standards according to Prader (Prader A, Largu RH, Molinari L, Issler C. Acta Paediatr 1998;52:1-125), extrapolated for prepubertal children (Preece, In Halliday MA, Barrett TM, Vernier RL, eds. Paediatric Nephrology. Baltimore: Williams and Wilkins, 1986:14-30).

Values are ± SD

Children receiving daily injections of r-hGH (both treatment-naïve and previously treated with pituitary-derived hGH) demonstrated a higher growth rate than those receiving three injections per week (Group 1 vs Group 2; $p<0.001$).

An extension study assessed growth response in 69 prepubertal children (19 girls) with idiopathic (n=48) or organic (n=21) growth hormone deficiency receiving r-hGH (SAIZEN) 0.6 IU/kg/week (0.2 mg/kg/week) via three subcutaneous injections. The initial treatment period (2 years), as described above, was followed by an optional extended treatment period during which the total weekly dose of r-hGH was unchanged; however, in most cases, dosing frequency increased to six or seven times per week. The mean duration of treatment was 64.4 months (range 1.2 – 140.9 months). The median H SDS at the start of the study was -3.8, and this improved significantly to -3.3 ($p < 0.001$) during the first year after the start of r-hGH therapy; this improvement was maintained throughout the study, resulting in a median value of -1.5 H SDS after 7 years of SAIZEN therapy. During the first year of r-hGH treatment, the median HV of patients was 8.5 cm/year (-2.8 SDS). During treatment years 2 – 7, patients' median HVs ranged between 5.5 and 6.7 cm/year (1.0 – 1.8 SDS). Bone age (BA) did not advance rapidly in response to treatment with r-hGH (1.3 ± 1.0 years/year, compared to 1.4 ± 0.3 years/year in change of height age (HA).

All studies conducted in prepubertal or pubertal children with inadequate endogenous growth hormone secretion (five studies) demonstrated the safety of somatropin and confirmed the known safety profile. Two patients developed anti-hGH antibodies. In both cases, the antibodies did not have any growth inhibiting effect. None of the patients developed antibodies to host cell protein. Three transfer patients who had anti-h-GH antibodies prior to treatment became negative within 6 months of treatment with SAIZEN.

**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 $2^{nd}$ X chromosome or chromosome aberrations, chronological age (CA) > 5 years, BA < 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/$m^2$/week SAIZEN increasing to 24 IU/$m^2$/week after the first year. Group 2 received 18 IU/$m^2$/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/$m^2$/week for all groups and two further subgroups were formed: (1a) who received 24 IU/$m^2$/week SAIZEN and 0.05 mg/kg/day oxandrolone and (2a) who stopped oxandrolone treatment and received 24 IU/$m^2$/week SAIZEN alone.

Results

This study demonstrated efficacy in HV, H 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 ± 7.1cm, 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 3).

**Table 3: Lean Body Mass (kg) by DXA**

| | SAIZEN (n=52) | Placebo (n=51) |
|---|---|---|
| LBM Baseline (kg) (mean) | 47.7 ± 11.4 | 54.0 ± 12.0 |
| Change from baseline at 6 months (LBM, kg) (mean) | + 1.9 ± 2.2 | – 0.2 ± 2.3 |
| 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 $VO_{2max}$ 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 LBM and fat mass achieved during initial treatment were maintained.

**Chronic Renal Insufficiency (CRI)**

Evidence of the safety and effectiveness of SAIZEN for the treatment of growth disturbance due to CRI is provided by the results of analysis of data from a study (4941) conducted with SAIZEN and published studies of clinical experience with r-hGH identified via a systematic literature review.

Study 4941

An open-label, multicentre study was conducted to evaluate the safety and efficacy of SAIZEN for the treatment of growth failure in children with CRI. Patients with growth failure and CRI were included in the study. CRI was defined as patients with end-stage renal disease on dialysis, or 12 months post kidney transplant, or compensated renal insufficiency with glomerular filtration rate (GFR) ≤ 30 mL/min per 1.73 $m^2$. Growth failure was defined as height of at least 2 SD and growth velocity of at least 0.5 SD below the mean for CA. Each patient's pre-treatment growth period served as a control for subsequent treatment periods. Patients were treated with SAIZEN 28 IU/$m^2$/week (0.35 mg/kg/week), administered by daily subcutaneous injections for the first 3 years of treatment, which could be increased to 36 IU/$m^2$/week (0.45 mg/kg/week) from the fourth year of treatment onwards in patients demonstrating insufficient growth.

A preliminary analysis was performed at one and two year time points. The primary efficacy endpoints for this analysis included increase in HV as well as H SDS and HV SDS for CA, calculated from baseline to the study time points. The secondary endpoint included the change in linear growth relative to the change in skeletal maturation (ΔHA/ΔBA ratio), as a measure of the preservation or loss of potential final height. Sub-group analysis was undertaken in all parameters after stratifying the patients according to their renal status.

Long term analysis was performed following 8 years of treatment. The primary endpoint for the long term analysis was the change in H SDS for CA, calculated from baseline, at onset of puberty and at study endpoint, and stratified according to final height status and overall. The secondary end point included the change in HV SDS during SAIZEN treatment. Other efficacy endpoints included parental adjusted H SDS and mean actual height.

Results

*Preliminary analysis (1 and 2 years of treatment)*

A total of 81 children were included in the study. The mean (±SD) CA was 8.6 ± 3.9 years with a BA of 5.7 ± 3.0 years.

*Changes in Height Velocity (HV)*
After 12 months: Of the 63 children available for analysis, 59 (94%) experienced an increase over baseline in HV. Mean HV (±SD) increased by 4.4 ± 4.0 cm/year ($p<0.001$).
After 24 months: Of the 44 children available for analysis, 39 (89%) experienced a sustained increase over baseline in HV. The mean HV for this cohort was 7.5 ± 2.9 cm/year, an increase of 3.0 ± 3.6 cm/year over baseline ($p<0.001$).

*Changes in Height Standard Deviation Score (H SDS)*
After 12 months: Of the 63 children available for analysis, 55 (87%) experienced an increase over baseline in H SDS. Mean H SDS increased by 0.7 ± 0.7 ($p<0.001$).
After 24 months: In the 44 children available for analysis, 39 (89%) experienced a sustained increase over baseline in H SDS. The percentage of children achieving a normal H SDS increased by 43% (19 of 44). For the group as a whole, the mean H SDS increased by 1.2 ± 1.2 ($p<0.001$).

*Changes in Height Velocity Standard Deviation Score (HV SDS)*
After 12 months: Of the 54 children available for analysis, 52 (96%) experienced an increase over baseline in HV SDS. Mean HV SDS increased by 6.2 ± 5.0 ($p<0.001$).
After 24 months: Of the 36 children available for analysis, 34 (94%) experienced a sustained increase over baseline. Mean HV SDS increased by 3.4 ± 3.5 ($p<0.001$).

The ΔHA/ΔBA was 1.6 ± 2.2 after the first year and 1.1 ± 0.6 after the second year of treatment, suggesting an improvement in predicted final height.

*Analysis of Efficacy based on Renal Status*
In the sub-group analysis, data were available from 44 children after the second year of treatment. Of these 44 children, 24 were in the compensated group and 8 were in the dialysis group. Data from the first year of treatment showed a significant increase in HV by +5.7 ± 5.1 cm/year over baseline ($n=24$, $p<0.001$) in the compensated group, and +4.6 ± 7.5 cm/year over baseline ($n=8$, $p<0.001$) in the dialysis group. After two years of treatment, HV increased from 5.0 ± 4.3 at baseline to 8.0 ± 3.8 ($n=24$, $p<0.001$) in the compensated group, and from 4.6 ± 6.4 at baseline to 5.9 ± 5.6 ($n=8$, $p=0.211$) in the dialysis group.

H SDS increased significantly in the compensated group, from -3.9 ± 2.0 at baseline to -2.8 ± 1.9 after 12 months of treatment ($n=24$, $p<0.001$), to -2.1 ± 2.0 after 24 months of treatment ($n=24$, $p<0.001$). In the dialysis group, less pronounced increase was seen in H SDS, although it was still greater than the baseline (from -3.9 ± 3.0 to -3.2 ± 2.8 after 12 months treatment ($n=8$, $p<0.004$), to -3.0 ± 3.0 after 24 months treatment ($n=8$; $p=0.014$)).

In HV SDS, both compensated and dialysis groups experienced a significant increase after 12 months of treatment, from -2.1 ± 2.5 at baseline to 5.3 ± 4.8 (compensated, $n=20$, $p<0.001$), and from -2.0 ± 4.1 to 3.4 ± 7.9 (dialysis, $n=7$, $p<0.001$). After two years of treatment, a significant increase in HV SDS was still seen in the compensated group (from -2.1 ± 2.5 to 2.7 ± 4.3 ($n=20$, $p<0.001$)). However, the increase was less pronounced in the dialysis group (from -2.0 ± 4.1 to -0.5 ± 7.0 ($n=7$, $p=0.176$)).

In terms of secondary end-point, the ΔHA/ΔBA ratio in all groups was close to unity at baseline and was greater than 1.0 in all groups after 1 year of treatment reaching statistical significance in the compensated group.

*Follow up analysis (2-8 years of treatment)*

Longer term data were available from 31 patients who continued after 2 years of treatment and received between 2.2 and 7.8 years of treatment with SAIZEN (mean duration of study was 63.31 ± 18.26 months). Baseline was defined as the last recorded value before or on the day of inclusion.

Of the 31 patients, four patients reached final height (defined as HV < 2 cm/year and Tanner puberty score ≥ 4), 6 patients reached near-final height (defined as HV > 2cm/year, age >16 years (boys) or >14 years (girls) and 21 patients were in non-final height group. In the overall group, mean H SDS during SAIZEN treatment increased from -3.12 ± 1.22 at baseline to -1.83 ± 1.88 at onset of puberty and there was a further increase to -1.21 ± 1.73 at study end point.

According to final height status, the gain in H SDS from baseline to study end was the greatest in the non-final height group (2.16 ± 1.25, p<0.0001) compared to the final height (1.26 ± 0.40, p=0.1250) and the near final height (1.44 ±1.66, p=0.0625) groups.

**Children born small for gestational age (SGA)**

Evidence of the effectiveness and safety of SAIZEN for the treatment of growth disturbance in short children born SGA is supported by data from published studies of clinical experience with r-hGH identified via a systematic literature review and company-sponsored studies.

Publications identified from systematic literature review

The summaries of relevant trials identified by the systematic literature review in children born SGA (meeting the criteria of birth length and/or weight < -2 SDS, starting treatment aged >4 years and treated until attainment of adult height) using r-hGH treatment are provided below:

Campos-Martorell, et al (Endocrinol Diabetes Nutr 2021; 68: 612-620) carried out a retrospective, observational study to evaluate prepubertal and pubertal height gain in 78 short children born SGA (51 boys, 27 girls) treated with r-hGH from prepubertal age. They were followed to adult height attainment, considered when there was no change in height or change < 0.5 cm in two consecutive measures at 6 to 12-month intervals, and bone age was 15 to 16 years for boys and 13.5 to 14 years for girls. Median r-hGH dose was 0.033 mg/kg/day, mean (± SD) age at treatment start was 7.3 ± 2.0 years (boys), 6.0 ± 1.8 (girls) and mean H SDS was -3.3 ± 0.7 (boys) and -3.4 ± 0.7 (girls). The cohort was followed up for 11.6 ± 2.1 years (boys) and 11.3 ± 2.1 years (girls).

A progressive increase in H SDS was seen during r-hGH treatment, as shown in Table 4, with the greatest gain occurring during the prepubertal period. The children attained an adult height of -1.7 ± 0.7 SDS, corresponding to 165.8 ± 4.4 (boys) and -1.6 ± 1.0 SDS, corresponding to 153.5 ± 5.3 cm (girls).

**Table 4: Height Standard Deviation Score (H SDS) During r-hGH Treatment (Campos Martorell et al 2021)**

| | Boys (n=51) | Girls (n=27) |
|---|---|---|
| Baseline | –3.31 ± 0.7 | –3.48 ± 0.7 |
| 1 year of r-hGH treatment | –2.4 ± 0.7 | –2.6 ± 0.7 |
| 2 years of r-hGH treatment | –2.14 ± 0.5 | –2.1 ± 0.7 |
| Completion of r-hGH treatment | –1.5 ± 0.7 | –1.5 ± 0.9 |
| Adult height | –1.75 ± 0.7 | –1.69 ± 1.0 |

Values are mean ± SD

No statistically significant differences, except for age when r-hGH was initiated, were seen between boys and girls for any H SDS values, or for those born pre-term and term. The authors concluded that the response to r-hGH treatment in short children born SGA is heterogenous, so dose should be individualised and treatment should be started at young age.

Beisti Ortego, et al (Med Clin (Barc) 2020; 154: 289 – 294) carried out a retrospective study in 80 short children born SGA treated with r-hGH to assess adult height attained and factors that determine treatment response. Adult height was defined as the height reached by the patients at Tanner 5 stage (adult) with a growth rate below 2 cm/year in the last year and < 1

cm/year in the last 6 months. Children were tested for r-hGH secretory status at baseline. The dose of r-hGH used in the non-deficiency group (0.033 mg/kg/day) was higher than that used in the GH deficiency (GHD) group (0.027 mg/kg/day). The age at treatment onset was 10.06 ± 2.49 years, with H SDS of -2.59 ± 0.6 SDS. The average duration of treatment was 4.68 ± 2.24 years.

Average age at the end of treatment at adult height was 15.92 ±1.34 years and mean adult H SDS was –1.63 ± 0.65, with H SDS gain from baseline to adult height of 0.96 ±0.70. The H SDS gain was significantly ($p<0.05$) higher for patients who started treatment when prepubertal versus those who were pubertal, as shown in Table 5.

**Table 5: Adult Height Standard Deviation Score (H SDS) and Gain from r-hGH Treatment Start (Beisti Ortego et al 2020)**

| | Prepubertal | Pubertal | ≥2 years Prepubertal | <2 years Prepubertal |
|---|---|---|---|---|
| Adult H SDS | –1.49 ± 0.61 | –1.90 ± 0.64 [a] | –1.47 ± 0.53 | –1.53 ± 0.72 |
| H SDS gain | 1.19 ± 0.58 | 0.53 ± 0.69 [b] | 1.32 ± 0.50 | 0.99 ± 0.60 [c] |

Values are mean ± SD; [a] $p<0.05$ for prepubertal vs pubertal; [b] $p<0.001$ for prepubertal vs pubertal; [c] $p<0.05$ for ≥2 years vs <2 years prepubertal

Factors associated with greater adult height gain were lower height, weight and BMI at start of treatment, lower chronological and bone age with lower IGF-1 before treatment, greater distance to target height, higher growth velocity the first and second year of treatment, and higher height gain before and during puberty.

The authors concluded that r-hGH treatment was effective in improving adult height, with better results in children who started treatment when prepubertal, and response did not depend on pituitary GH status.

Arroyo Ruiz, et al (Ther Adv Endocrinol Metab 2022; 13: 1-14) carried out a prospective, longitudinal, observational study of 61 short children born SGA, treated with r-hGH and who reached adult height. The primary objective was to analyse the efficacy of r-hGH treatment by studying the factors affecting the final response to treatment assessed by adult height and height gain. Adult height was defined as growth rate < 2 cm/year. Treatment started before onset of puberty and the mean dose was 0.035 mg/kg/day. Mean (±SD) age at start of r-hGH treatment was 6.37 ± 1.79 years and 6.05 ± 1.83 years for boys (n=28) and girls (n=33), respectively. Baseline H SDS was -2.91 ± 0.62 (boys) and -3.22 ± 0.75 (girls).

A progressive increase in height was seen from the start to completion of r-hGH treatment, as shown in Table 6.

**Table 6: Height Standard Deviation Score (H SDS) During r-hGH Treatment (Arroyo Ruiz et al 2022)**

| | Boys (n=28) | Girls (n=33) |
|---|---|---|
| Start of r-hGH treatment | –2.91 ± 0.62 | –3.22 ± 0.75 |
| 1 year of r-hGH treatment | –2.36 ± 0.69 | –2.55 ± 0.72 |
| 1 year H SDS gain | 0.54 ±0.38 | 0.66 ± 0.42 |
| Growth velocity in the first year (SDS) | 2.51 ± 1.86 | 2.53 ± 2.94 |
| H SDS at puberty onset | –1.19 ± 0.61 | –1.51 ± 0.80 |
| H SDS gain to puberty onset | 1.71 ± 0.83 | 1.70 ± 1.06 |
| Adult height | –1.94 ± 0.94 | –1.72 ± 0.68 |

Values are mean ± SD

H SDS did not differ significantly between boys and girls at any point. Of the initial 96 patients, 61 patients (28 boys and 33 girls) reached adult height. Adult H SDS gain from treatment start was 0.99 ± 0.8 and 1.49 ± 0.94 for boys and girls, respectively ($p<0.008$). Adult height (SDS) was within the normal range (> -2) for 53% of boys and 75% of girls, although there was no significant difference in adult H SDS between genders ($p>0.05$). The pubertal height gain was 22.6 ± 5.8 cm in boys and 18.8 ± 4.5 cm in girls.

The authors concluded that the H SDS gain in the first year is the most important factor in determining r-hGH treatment response, followed by the difference from mid-parental H SDS at start of treatment.

Dahlgren, et al (Pediatr Res 2005; 57: 216 – 222) carried out an observational study of 77 short children born SGA, treated with r-hGH until adult height, with the aim to assess long-term growth response. Treatment started before onset of puberty, at a dose of 0.033 mg/kg/day. During puberty, 24 children (17 males/7 females) were randomised to a dose of 0.066 mg/kg/day. A comparator group comprised 34 short children born SGA who did not receive r-hGH treatment. r-hGH treatment was stopped at adult height when growth velocity was <1 cm/year and height was monitored for at least 2 more years.

Mean age at start of treatment was 10.7 ± 2.5 years and H SDS was -2.8 ± 0.7.

The final height of 86% of the r-hGH treated children was within their target height (i.e., ≥ -1 SDS from their mid-parental height), compared with only 52% of the untreated group ($p<0.001$). The mean gain in H SDS from the start of treatment to final height was 1.3 SD ± 0.8 (corresponding to 9 cm). Among those treated for > 2 prepubertal years, mean gain was 1.7 SDS ± 0.7 (12 cm), and for those treated <2 prepubertal years the gain was 0.9 SDS ± 0.7 (6 cm) ($p<0.001$).

It was concluded that r-hGH could normalise adult height and height gain before puberty and was maintained to adult height.

Renes, et al (Clin Endocrinol 2015; 82: 854 – 864) conducted an open-label, longitudinal study of 170 short children born SGA treated with r-hGH, to investigate the efficacy of r-hGH treatment on adult height and assess the relationship of catch-up growth and pubertal growth with adult H SDS attained. At the start of treatment, the children were either prepubertal or early pubertal, with median age of 7.1 years (interquartile range (IQR): 5.4 to 9.4) and median H SDS of -3.0 (IQR: -3.4 to -2.5). The r-hGH treatment dose was 1 mg/m$^2$/day (0.033

mg/kg/day), adjusted every 3 months according to body surface area. In girls < 11 years and boys < 12 years, with a relatively short height at the onset of puberty, puberty was postponed for 2 years using a gonadotropin releasing hormone analogue (GnRHa) in addition to r-hGH treatment (n=29). Adult height was defined as growth rate <0.5 cm in the previous 6 months.

In the adult height ITT analyses, mean (SDS) adult height for 83 boys was 170.8 (6.8) cm, corresponding to -1.9 (1.0) SDS. The target height-corrected adult height was -1.2 (0.9) SDS. Mean adult height for 87 girls was 158 (5.8) cm, corresponding to -1.9 (0.9) SDS. The target height-corrected adult height was -1.4 (0.9 SDS).

In the adult height uncensored cases analyses, adult height was reached in 136 children (66 boys)/70 (girls). Median age at adult height was 17.4 (IQR: 16.6 to 18.1) years for boys, after 9.6 (7.5 to 11.1) years of treatment. For girls, median age was 15.7 (IQR: 14.9 to 16.3) years, after 9.0 (7.0 to 10.2) years of treatment. Adult H SDS was -1.8 (-2.5 to -1.2) and -1.9 (-2.4 to -1.1) for boys and girls, respectively. The adult H SDS difference from mid-parental H SDS was within the normal range of >-2 for 73% of the children overall, 76% of the 107 children who received r-hGH only and 60% of the 29 who received r-hGH plus GnRHa.

At puberty, H SDS declined with -0.4 (-0.9 to 0.3) SDS in boys and -0.5 (-0.8 to 0.2) SDS in girls. This resulted in a significantly lower total height gain SDS compared to the prepubertal height gain SDS ($p<0.001$).

It was concluded that in short children born SGA, adult height was improved by treatment with r-hGH with better gain when starting at a younger age. However, H SDS declined from mid-puberty due to an early reduction in growth velocity.

A meta-analysis conducted by Maiorana and Cianfarani (Pediatrics 2009; 124: e519-e531) examined the evidence of long-term r-hGH treatment in short children born SGA. Four randomised controlled trials comprising 270 treated children and 155 untreated children treated to attainment of adult height were included in the meta-analysis. Mean ± SD age at start of study was 8.6 ± 0.8 years (range 7.9 to 10.7). The dose of r-hGH was either 0.033 or 0.067 mg/kg/day and the mean duration of r-hGH treatment was 7.3 ± 0.35 years.

The meta-analysis found that mean adult height gain of the r-hGH treated group significantly exceeded controls by 0.9 SDS (5.7 cm) ($p<0.0001$). Mean gain in adult H SDS was 1.5 (9.4 cm) for treated children compared with 0.25 (1.6 cm) for untreated children ($p<0.0001$). When corrected for mid-parental height, mean adult H SDS was -0.46 in the treated group versus -1.26 for the untreated group ($p<0.0001$). The overall mean H SDS corrected for mid-parental height was 1.46 (9.2 cm) in the treated group versus 0.4 (2.5 cm) in the untreated group ($p<0.0001$). No significant difference in adult height was observed between the two r-hGH dose regimens.

Company-sponsored Studies

The evidence from company-sponsored studies in children born SGA (meeting the criteria of birth length and/or weight < -2 SD, starting treatment aged > 4 years and treated with higher doses and different dose regimens) (Studies GF 4001, GF 6283, IMP 20184) showed consistent results of r-hGH treatment to improve the mean and median H SDS and HV SDS.

## 5.2. PHARMACOKINETIC PROPERTIES

After intramuscular injection of 4 IU somatropin/$m^2$ body surface area, $C_{max}$ (36.9 ± 12.1 ng/mL) was measured at 3 hours ($T_{max}$). hGH levels returned to pre-injection levels after 12 hours. The $AUC_{24}$ was 183 ng.h/mL. These pharmacokinetic parameters are similar to those reported in the literature for pituitary-derived hGH. After subcutaneous injection, $C_{max}$ was delayed until 4 – 6 hours post injection. The $AUC_{24}$ 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.

## 5.3. PRECLINICAL SAFETY DATA

### 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.

### 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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS

See Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

## 6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or identified as part of the registration of this medicine.

## 6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. Do not use after the expiry date.

**SAIZEN solution for injection**
SAIZEN solution for injection should be used with the dedicated autoinjector devices provided separately. After the first injection, the contents of the cartridge should be used within 28 days. After first injection, should refrigeration be temporarily unavailable, the

Saizen cartridge in the dedicated autoinjector devices can be stored for up to 7 days at or below 25 °C (outside a refrigerator). Following this, the Saizen cartridge must be returned to the refrigerator and stored at 2°C to 8°C (Refrigerate. Do not freeze) and still used within 28 days after the first injection.

## 6.4. SPECIAL PRECAUTIONS FOR STORAGE

**SAIZEN solution for injection**
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.

## 6.5. NATURE AND CONTENTS OF CONTAINER

**SAIZEN solution for injection** is supplied in packs of 1 or 5[§] glass cartridges for multidose use in one patient only.

[§] Not currently marketed.

## 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7. PHYSICOCHEMICAL PROPERTIES

SAIZEN is a recombinant human growth hormone (r-hGH) 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 international units (IU) equals 1 mg somatropin (rmc) by weight. The dose in mg set out below is based on this equivalence.

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

## 8. SPONSOR

*SAIZEN is supplied in Australia by:*

Merck Healthcare Pty Ltd
Suite 1, Level 1, Building B
11 Talavera Road
Macquarie Park NSW 2113
E-mail: medinfo.australia@merckgroup.com
Phone: 1800 633 463

## 9. DATE OF FIRST APPROVAL

SAIZEN solution for injection: 22 August 2011

## 10. DATE OF REVISION

18 May 2026

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 4.4 | Additional precautionary text for slipped capital femoral epiphysis and osteonecrosis of the femoral head.<br>Additional statement on growth spurts which may increase the risk of joint-related problems. |
| 4.8 | Addition of adverse reaction “avascular necrosis of the femoral head (incl. Legg-Calve-Perthes disease)”.<br>Revised frequency for “Slipped capital femoral epiphysis (epiphysiolysis capitis femoris)” from “very rare” to “frequency not known”. |