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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAIZEN® safely and effectively. See full prescribing information for SAIZEN.

SAIZEN [somatropin (rDNA origin) for injection], for subcutaneous use

Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

SAIZEN is a recombinant human growth hormone indicated for:
Pediatric: Treatment of children with growth failure due to growth hormone deficiency (GHD) (1.1)
Adult: Treatment of adults with either adult onset or childhood onset GHD. (1.2)

DOSAGE AND ADMINISTRATION

- **Pediatric GHD:** 0.18 mg/kg/week, divided into equal doses given either on 3 alternate days, 6 times per week or daily (2.1)
- **Adult GHD:** Either a non-weight based or a weight based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-1 concentrations (2.2)
  Non-weight-based dosing: A starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day (2.2)
  Weight-based dosing: The recommended initial dose is not more than 0.005 mg/kg/day; the dose may be increased as tolerated to not more than 0.01 mg/kg/day after 4 weeks (2.2)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

DOSAGE FORMS AND STRENGTHS

- SAIZEN lyophilized powder in vial (3): 5 mg and 8.8 mg
- SAIZEN click.easy® reconstitution device: One vial SAIZEN containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection
- saizenprep® reconstitution device: One vial SAIZEN containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection

CONTRAINDICATIONS

- Acute Critical Illness (4)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment – reports of sudden death (4)
- Active Malignancy (4)
- Hypersensitivity to somatropin or excipients (4)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4)
- Children with closed epiphyses (4)

WARNINGS AND PRECAUTIONS

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1)
- Prader-Willi syndrome in Children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment. Discontinue treatment if these signs occur (5.2)
- Neoplasms: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin—in particular meningiomas as in patients treated with radiation to the head for their first neoplasm (5.3)
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4)
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5)
- Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.6)
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.7)
- Hypoadrenalism: Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (5.8)
- Hypothyroidism: May first become evident or worsen (5.9)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.10)
- Progression of Preexisting Scoliosis: May develop (5.11)
- Reevaluation of Childhood Onset Adult GHD (5.12)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.15)
- Benzyl Alcohol (5.16)

ADVERSE REACTIONS

Most common adverse reactions are injection site reactions (such as pain, numbness, redness, and swelling), fluid retention, peripheral edema, arthralgia, myalgia, paresthesia, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext 5563 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1)
- Glucocorticoid Replacement: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral/Injectable Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION
Revised: 1/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

SAIZEN [somatropin (rDNA origin) for injection] is indicated for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone.

1.2 Adult Patients

SAIZEN is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

Adult Onset

Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood Onset

Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for growth hormone deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. Confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection.

SAIZEN therapy should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth hormone deficiency or adult patients with either childhood-onset or adult-onset growth hormone deficiency.

2.1 Pediatric Growth Hormone Deficiency (GHD)

SAIZEN dosage and administration schedule should be individualized for each patient. The recommended weekly dosage is 0.18 mg/kg of body weight by subcutaneous injection. It should be divided into equal doses given either on 3 alternate days, 6 times per week or daily.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human growth hormone.

Treatment with SAIZEN of growth failure due to growth hormone deficiency should be discontinued when the epiphyses are fused.

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2.2 Adult Growth Hormone Deficiency (GHD)

Either of two approaches to SAIZEN dosing may be followed: a weight-based regimen or a non-weight-based regimen.

Weight-based

Based on the dosing utilized in the original pivotal study described herein, the recommended dosage at the start of therapy is not more than 0.005 mg/kg given as a daily subcutaneous injection. The dosage may be increased to not more than 0.01 mg/kg/day after 4 weeks according to individual patient requirements. Clinical response, side effects, and determination of age-and gender-adjusted serum insulin-like growth factor (IGF-1) levels may be used as guidance in dose titration.

Non-weight-based

Alternatively, taking into account more recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-1 concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse reactions and/or serum IGF-1 levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

Prior to self-administration of the product at home, ensure to train patients and caregivers how to prepare and administer the product correctly to help avoid wrong technique and dosing errors.

Vials

To prevent possible contamination, wipe the rubber vial stopper with an antiseptic solution before puncturing it with the needle. It is recommended that SAIZEN be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

After determining the appropriate patient dose, reconstitute each vial of SAIZEN as follows: 5 mg vial with 1 to 3 mL of Bacteriostatic Water for Injection, USP (Benzyl Alcohol preserved); 8.8 mg vial with 2-3 mL of Bacteriostatic Water for Injection, USP (Benzyl Alcohol preserved). Approximately 10% mechanical loss can be associated with reconstitution and multidose administration.

If sensitivity to the diluent occurs, SAIZEN may be reconstituted with Sterile Water for Injection, USP. When SAIZEN is reconstituted in this manner, the reconstituted solution should be used immediately and any unused solution should be discarded *[see Warnings and Precautions (5.15)]*.

To reconstitute SAIZEN, inject the diluent into the vial of SAIZEN aiming the liquid against the glass vial wall. Swirl the vial with a GENTLE rotary motion until contents are dissolved completely. DO NOT SHAKE. Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. SAIZEN MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

click.easy® cartridges

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For drug preparation instructions for SAIZEN click.easy® cartridges, please refer to the instructions for use provided with click.easy® reconstitution device.

saizenprep® cartridges

For drug preparation instructions for saizenprep® cartridges, please refer to the Instructions for Use provided with saizenprep® reconstitution device.

Injection sites should always be rotated to avoid lipoatrophy.

3 DOSAGE FORMS AND STRENGTHS

SAIZEN lyophilized powder (to be reconstituted with Bacteriostatic Water for Injection):

- 5 mg per vial
- 8.8 mg per vial

SAIZEN click.easy® reconstitution device:

- One vial SAIZEN containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection

saizenprep® reconstitution device:

- One vial SAIZEN containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection

4 CONTRAINDICATIONS

• Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure *[see Warnings and Precautions (5.1)]*.

• Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment *[see Warnings and Precautions (5.2)]*. There have been reports of sudden death when somatropin was used in such patients. SAIZEN is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

• Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any pre-existing malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor *[See Warnings and Precautions (5.3)]*.

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- **Hypersensitivity**

SAIZEN is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products *[see Warnings and Precautions (5.6)]*.

- **Diabetic Retinopathy**

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

- **Closed Epiphyses**

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

- **Benzyl Alcohol**

SAIZEN reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) should not be administered to patients with a known sensitivity to Benzyl Alcohol *[see Warnings and Precautions (5.16)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin *[see Contraindications (4)]*. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

5.2 Prader-Willi Syndrome in Children

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively *[see Contraindications (4)]*. SAIZEN is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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5.3 Neoplasms

In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence *[see Contraindications (4)]*. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be monitored carefully for development of neoplasms.

Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes of preexisting nevi.

5.4 Glucose Intolerance/Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment and new onset type 2 diabetes mellitus has been reported in patients. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

5.5 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH.

5.6 Severe Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs *[see Contraindications (4)]*.

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5.7 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention (e.g. edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias) are usually transient and dose dependent.

5.8 Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment *[see Section 7.1, 11-β Hydroxysteroid Dehydrogenase Type 1]*.

5.9 Hypothyroidism

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

5.10 Slipped Capital Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

5.11 Progression of Preexisting Scoliosis in Pediatric Patients

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

5.12 Reevaluation of Childhood Onset Adult GHD

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. Experience with prolonged treatment in adults is limited.

5.13 Lipoatrophy

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site *[see Dosage and Administration (2.3)]*.

5.14 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and IGF-1 may increase with somatropin therapy.

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5.15 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin–treated patient, especially a child, who develops persistent severe abdominal pain.

5.16 Benzyl Alcohol

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

6 ADVERSE REACTIONS

The following important adverse reactions are also described elsewhere in the labeling:

- Increased mortality in patients with acute critical illness *[see Warnings and Precautions (5.1)]*
- Fatalities in children with Prader-Willi syndrome *[see Warnings and Precautions (5.2)]*
- Neoplasms *[see Warnings and Precautions (5.3)]*
- Glucose intolerance and diabetes mellitus *[see Warnings and Precautions (5.4)]*
- Intracranial hypertension *[see Warnings and Precautions (5.5)]*
- Severe hypersensitivity *[see Warnings and Precautions (5.6)]*
- Fluid retention *[see Warnings and Precautions (5.7)]*
- Hypoadrenalism *[see Warnings and Precautions (5.8)*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*
- Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.10)]*
- Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.11)]*
- Lipoatrophy *[see Warnings and Precautions (5.13)]*
- Pancreatitis *[see Warnings and Precautions (5.15)]*
- Benzyl alcohol *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

Growth Hormone Deficient Pediatric Patients

In clinical studies in which SAIZEN was administered to growth hormone deficient children, the following reactions were infrequently seen: local reactions at the injection site (such as pain, numbness,

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redness and swelling), hypothyroidism, hypoglycemia, seizures, exacerbation of preexisting psoriasis and disturbances in fluid balance.

Growth Hormone Deficient Adult Patients

For a description of the clinical trials refer to section 14. During the 6-month placebo-controlled study, adverse reactions were reported in 56 patients (93.3%) in the somatropin-treated group and 42 patients (76.4%) in the placebo-treated group. Adverse reactions with an incidence of ≥5% in SAIZEN-treated patients which were more frequent in SAIZEN-treated patients compared with placebo-treated patients are listed in Table 1. Arthralgia, myalgia, peripheral edema, other types of edema, carpal tunnel syndrome, paraesthesia and hypoaesthesia were common in the somatropin-treated patients and reported more frequently than in the placebo group. These types of adverse reactions are thought to be related to the fluid accumulating effects of somatropin. During the placebo-controlled portion of the study, approximately 10% of patients without preexisting diabetes mellitus or impaired glucose tolerance treated with somatropin manifested mild, but persistent, abnormalities of glucose tolerance, compared with none in the placebo group. During the open label phase of the study, approximately 10% of patients treated with somatropin required a small upward adjustment of thyroid hormone replacement therapy for preexisting central hypothyroidism and 1 patient was newly diagnosed with central hypothyroidism. In addition, during the open label phase of the study, when all patients were being treated with somatropin, two patients with preexisting central hypoadrenalism required upward titration of hydrocortisone maintenance therapy which was considered to be suboptimal (unrelated to intercurrent stress, surgery or disease), and 1 patient was diagnosed *de novo* with central adrenal insufficiency after six months of somatropin treatment. Anti-GH antibodies were not detected.

Table 1 Adverse Reactions with ≥5% Overall Incidence in SAIZEN-Treated Patients Which Were More Frequent in SAIZEN-Treated Patients Compared with Placebo-Treated Patients During a 6 Month Study

Adverse Reaction	SAIZEN-Treated (N=60)	Placebo (N=55)
Arthralgia	14(23.3%)	7(12.7%)
Headache	11(18.3%)	8(14.5%)
Edema peripheral	9(15.0%)	2(3.7%)
Myalgia	5(8.3%)	2(3.6%)
Paraesthesia	4(6.7%)	1(1.8%)
Hypoaesthesia	4(6.7%)	0
Edema dependent	3(5.0%)	2(3.6%)
Skeletal Pain	3(5.0%)	1(1.8%)
Carpal tunnel syndrome	3(5.0%)	1(1.8%)
Edema generalized	3(5.0%)	0
Chest pain	3(5.0%)	0
Depression	3(5.0%)	0
Hypothyroidism	3(5.0%)	0
Insomnia	3(5.0%)	0

N = number of patients

The adverse reaction pattern observed during the open label phase of the study was similar to the one presented above.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by

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several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SAIZEN with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was observed.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of SAIZEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products *[See Warnings and Precautions (5.6)]*.

Leukemia has been reported in a small number of growth hormone deficient patients treated with growth hormone. It is uncertain whether this increased risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors. So far, epidemiological data fail to confirm the hypothesis of a relationship between growth hormone therapy and leukemia.

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children and adults) *(see Warnings and Precautions [5.14]).*

7 DRUG INTERACTIONS

7.1 Inhibition of 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1 *[see Warnings and Precautions (5.8)]*.

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.

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7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages *[see Dosage and Administration (2.2)]*.

7.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 31 and 62 times, respectively, the human (child) weekly dose based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to SAIZEN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether SAIZEN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SAIZEN is administered to a nursing woman.

8.5 Geriatric Use

The safety and effectiveness of SAIZEN in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of SAIZEN, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients *[see Dosage and Administration (2.2)]*.

8.6 Hepatic Impairment

A reduction in somatropin clearance has been noted in patients with hepatic dysfunction as compared with normal controls. However, no studies have been conducted for SAIZEN in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Subjects with chronic renal failure tend to have decreased clearance of somatropin compared to those with normal renal function. However, no studies have been conducted for SAIZEN in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

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8.8 Gender Effect

In adults, the clearance of somatropin in both men and women tends to be similar. No gender studies have been performed in children.

10 OVERDOSAGE

Short-term
Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Moreover, overdose with somatropin is likely to cause fluid retention.

Long-term
Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

11 DESCRIPTION

SAIZEN is a human growth hormone produced by recombinant DNA technology. SAIZEN has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone. SAIZEN is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human growth hormone gene.

SAIZEN is a sterile, non pyrogenic, white, lyophilized powder intended for subcutaneous injection after reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). The reconstituted solution has a pH of 6.5 to 8.5.

Vials

SAIZEN is available in 5 mg and 8.8 mg vials. The quantitative composition per vial is:

5 mg vial:
Each vial contains 5.0 mg somatropin, 34.2 mg sucrose and 1.16 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

8.8 mg vial:
Each vial contains 8.8 mg somatropin, 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

Diluent
The diluent is Bacteriostatic Water for Injection, USP containing 0.9% Benzyl Alcohol added as an antimicrobial preservative.

Reconstitution devices:

click.easy® reconstitution device
SAIZEN 8.8 mg vial contained in the click.easy® reconstitution device.
Each vial contains 8.8 mg somatropin, 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

Diluent
The diluent contained in click.easy® device is 0.3% (w/v) metacresol in Sterile Water for Injection added as an antimicrobial preservative. The reconstituted solution has a pH of 6.5 to 8.5.

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saizenprep® reconstitution device
SAIZEN 8.8 mg vial supplied with the saizenprep® reconstitution device. Each vial contains 8.8 mg somatropin, 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

Diluent
The diluent supplied with saizenprep® reconstitution device is 0.3% (w/v) metacresol in Sterile Water for Injection added as an antimicrobial preservative. The reconstituted solution has a pH of 6.5 to 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Somatropin (as well as endogenous growth hormone) binds to dimeric growth hormone receptors located within the cell membranes of target tissue cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-1 produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) *[see Pharmacodynamics (12.2)]*.

12.2 Pharmacodynamics

Tissue Growth

Skeletal Growth: SAIZEN stimulates skeletal growth in prepubertal children with pituitary growth hormone deficiency. Skeletal growth is accomplished at the epiphyseal plates at the ends of long bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by growth hormone and one of its mediators, insulin-like growth factor-1. Serum levels of insulin-like growth factor-1 (IGF-1) are low in children and adolescents who are growth hormone deficient, but increase during treatment with SAIZEN. Linear growth continues until the growth plates fuse at the end of puberty.

Cell Growth: Treatment with pituitary-derived human growth hormone results in an increase in both the number and the size of skeletal muscle cells.

Organ Growth: Somatropin influences the size and function of internal organs and increases red cell mass.

Protein Metabolism
Linear growth is facilitated in part by increased cellular protein synthesis. This is reflected by increased cellular uptake of amino acids and nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during somatropin therapy.

Carbohydrate Metabolism
Somatropin is a modulator of carbohydrate metabolism. Children with inadequate secretion of growth hormone sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. SAIZEN therapy may decrease glucose tolerance. Administration of SAIZEN to normal adults and patients with growth hormone deficiency resulted in transient increases in mean serum fasting and postprandial insulin levels. However, glucose levels remained in the normal range.

Lipid Metabolism
Acute administration of somatropin to humans results in lipid mobilization. Nonesterified fatty acids increase in plasma within one hour of SAIZEN administration. In growth hormone deficient patients, long-term somatropin administration often decreases body fat. Mean cholesterol levels decreased in patients treated with SAIZEN. The clinical significance of this decrease in cholesterol level is unknown.

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Mineral Metabolism
Somatropin administration results in the retention of total body potassium, phosphorus, and sodium. Serum calcium levels appear to be unaffected.

Connective Tissue/Bone Metabolism
Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

12.3 Pharmacokinetics

Absorption - The absolute bioavailability of somatropin after subcutaneous administration ranges between 70 to 90%.

Distribution - The steady-state volume of distribution (mean ±SD) of somatropin following intravenous administration in healthy volunteers was estimated to be 12.0 ± 1.08 L.

Metabolism - The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products is returned to the systemic circulation. The mean half-life of intravenous somatropin in normal males is around 0.6 hours, whereas subcutaneously and intramuscularly administered somatropin has a half-life of around 2 hours. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

Excretion - The clearance (mean ±SD) of intravenously administered somatropin in six normal male volunteers was 14.6 ± 2.8 L/hr.

Specific Populations

Pediatric - The pharmacokinetics of somatropin is similar in children and adults. However, no pharmacokinetic studies of SAIZEN have been conducted in pediatric patients.

Gender - No gender studies have been performed in children for somatropin. In adults, the clearance of somatropin in both men and women tends to be similar. However, no studies have been conducted to evaluate the effect of gender on pharmacokinetics of SAIZEN**.**

Race - No studies have been conducted to determine the effect of race on the pharmacokinetics of SAIZEN.

Renal Impairment- Children and adults with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of SAIZEN.

Hepatic Impairment - A reduction in somatropin clearance has been noted in patients with hepatic dysfunction as compared with normal controls.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies for carcinogenicity have not been performed with SAIZEN. There is no evidence from animal studies to date of SAIZEN-induced mutagenicity or impairment of fertility.

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14 CLINICAL STUDIES

Adult Growth Hormone Deficiency (GHD)
A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted in 115 adults with growth hormone deficiency 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 change from baseline in lean body mass measured by dual energy X-ray absorptiometry (DXA) after 6 months. Treatment with SAIZEN produced significant ($p<0.001$) increases from baseline in LBM compared to placebo (Table 2).

Table 2 – Lean Body Mass (kg) by DXA

	SAIZEN (n=52)	**Placebo (n=51)**
Baseline (mean)	47.7	54.0
Change from baseline at 6 months (mean)	+1.9	-0.2
Treatment difference (mean) 95% confidence interval p-value	2.1 (1.3, 2.9) <0.001	

Sixty-seven (58%) of the 115 randomized patients were male. The adjusted mean treatment difference on the increase in lean body mass from baseline was significantly greater in males (2.9 kg) than females (0.8 kg).

Ninety-seven (84%) of the 115 randomized patients had adult onset GHD. The adjusted mean treatment differences on the increase in lean body mass from baseline were not significantly different in AO GHD (2.1 kg) compared with childhood onset GHD (1.0 kg) patients. However, there were relatively few patients with childhood onset GHD (n=18) on which to base the comparison.

Analysis of the treatment difference on the change from baseline in total fat mass (by DXA) revealed a significant decrease ($p<0.001$) in the SAIZEN-treated group compared to the placebo group. SAIZEN also produced beneficial effects on several bone turnover markers including bone specific alkaline phosphatase, C-terminal propeptide, osteocalcin, urine deoxypyridinoline and iPTH.

One hundred and eleven patients were enrolled in an open label follow up study and treated with SAIZEN for an additional 6-30 months. During this period, the beneficial effects on lean body mass and total fat mass achieved during the initial six months of treatment were maintained.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SAIZEN can be administered using (1) a standard sterile disposable syringe and needle, (2) a compatible SAIZEN needle-free injection device or (3) a compatible SAIZEN needle injection device. For proper use, refer to the Instructions for Use provided with the administration device.

SAIZEN is a sterile, non pyrogenic, white, lyophilized powder supplied in packages containing:

1 vial of 5 mg SAIZEN and 1 vial of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1005-2

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1 vial of 8.8 mg SAIZEN and 1 vial of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1088-1

1 click.easy® cartridge of 8.8 mg SAIZEN and 1.51 mL Sterile Water for Injection 0.3% (w/v) metacresol as a antimicrobial preservative NDC 44087-1080-1

1 saizenprep® cartridge of 8.8 mg SAIZEN and 1.51 mL Sterile Water for Injection 0.3% (w/v) metacresol as antimicrobial preservative NDC 44087-0016-1

16.2 Storage and Handling

Before Reconstitution - SAIZEN should be stored at room temperature (15°-30°C/59°-86°F). Expiration dates are stated on the labels.

After Reconstitution - SAIZEN 5 mg and 8.8 mg vials reconstituted with the Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) provided should be stored under refrigeration (2°–8°C/36°–46°F) for up to 14 days.

SAIZEN 8.8 mg click.easy® cartridge reconstituted with the Sterile Water for Injection, 0.3% (w/v) metacresol provided should be stored under refrigeration (2°–8°C/36°–46°F) for up to 21 days.

SAIZEN 8.8 mg saizenprep® cartridge reconstituted with the Sterile Water for Injection, 0.3% (w/v) metacresol provided should be stored under refrigeration (2°-8°C/36°-46°F) for up to 21 days.

Avoid freezing reconstituted vials or cartridges of SAIZEN.

17 PATIENT COUNSELING INFORMATION

Prior to self-administration of the product at home, ensure to train patients and caregivers how to prepare and administer the product correctly to help avoid wrong technique and dosing errors.

Patients being treated with SAIZEN (and/or their parents) should be informed about the potential benefits and risks associated with SAIZEN treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer SAIZEN should receive appropriate training and instruction on the proper use of SAIZEN from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

To reconstitute SAIZEN, inject the diluent into the vial of SAIZEN aiming the liquid against the glass vial wall. Swirl the vial with a GENTLE rotary motion until contents are dissolved completely. DO NOT SHAKE. Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. SAIZEN MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Never Share a SAIZEN Needle Between Patients

Counsel patients that they should never share a SAIZEN needle with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

For drug preparation instructions for SAIZEN click.easy® cartridges, please refer to the Instructions for Use provided with click.easy® reconstitution device.

For drug preparation instructions for saizenprep® cartridges, please refer to the Instructions for Use provided with saizenprep® reconstitution device.

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Manufactured for: EMD Serono, Inc., Rockland, MA 02370 USA

2017

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click.easy® Reconstitution Device
Saizen® [somatropin (rDNA origin) for injection] for injection, for subcutaneous use 8.8 mg

INSTRUCTIONS FOR USE

For complete dosing and safety information, please refer to the SAIZEN Package Insert.

COMPOSITION

Each vial of SAIZEN 8.8 mg contained in the 5.83 mg/mL click.easy® device contains the following ingredients:

- Active substance: Somatropin (Recombinant Human Growth Hormone) 8.8 mg.
- Excipients: Sucrose, Phosphoric acid, Sodium Hydroxide; 1 mL of the reconstituted SAIZEN solution contains 5.83 mg of somatropin when reconstituted with the contents of the diluent cartridge.

COMPOSITION OF DILUENT

Each cartridge of diluent contained in the click.easy® reconstitution device contains the following ingredients:

5.83 mg/mL click.easy®

Active substance: Metacresol USP (4.52 mg),

Excipients: Phosphoric acid 85% to adjust pH, Water for Injection, USP (1.51 mL)

Patients with a known sensitivity to any of the above active substances or excipients should avoid using this product.

PHARMACEUTICAL FORM

Powder and diluent for solution for injection: Powder and diluent (0.3% (w/v) metacresol in water for injection) for parenteral use.

METHOD AND ROUTE OF ADMINISTRATION

The product (powder in vials) must be reconstituted with the enclosed diluent (0.3% (w/v) metacresol in water for injection) using the click.easy® reconstitution device.

The reconstituted solution is intended for subcutaneous administration (under the skin) and should be clear with no particles. If the solution contains particles, it must not be injected.

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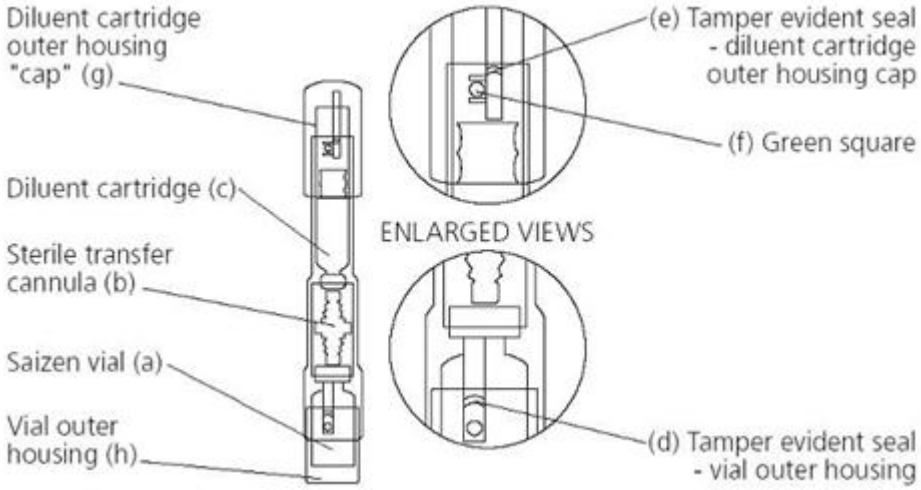
IMPORTANT INFORMATION

Patients should be thoroughly instructed in the reconstitution procedure.

For young children, the reconstitution process should be supervised by an adult.

For administration of SAIZEN 8.8 mg contained in the click.easy® device, please read the following instructions carefully. Please consult your doctor, nurse or pharmacist if you have any questions concerning the reconstitution process.



Check that the click.easy® reconstitution device contains an unused SAIZEN vial (a) and an unused diluent cartridge (c).

Do NOT use the device if the vial or cartridge appear empty or used and return it to your pharmacist or doctor.

Wash your hands with soap and water.

HOW TO PREPARE YOUR SOLUTION OF SAIZEN®

1. Place the click.easy® device vertically on a clean flat surface with the SAIZEN vial on the bottom and the diluent cartridge outer housing cap (g) on top facing upward.
2. Push on the top diluent cartridge outer housing cap (g) firmly until the SAIZEN vial outer housing (h) is completely inside the main body. This step breaks the tamper evident seal on the vial.
3. Turn the diluent cartridge outer housing cap (g) clockwise until the green square (f) is visible at the lower end of the narrow rectangular opening. Push the diluent cartridge outer housing cap down very slowly until it will go no further and the green colored square appears at the upper end of the narrow rectangular opening.
4. Check that all the diluent has been transferred into the vial. Dissolve the SAIZEN powder with the diluent by gently swirling the click.easy® device (Note: Do not transfer the diluent forcefully or shake the click.easy® device. A fast transfer of the diluent or shaking

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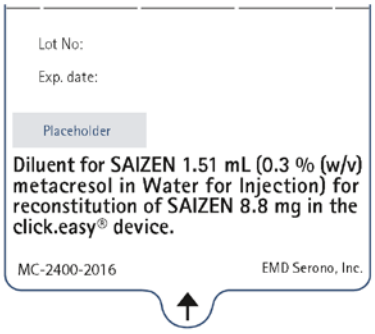
of the click.easy® device will create more foam). Let the solution stand for 2-5 minutes until the SAIZEN powder is completely dissolved.

5. Turn the click.easy® device upside down so the SAIZEN vial is now on top and pull the diluent cartridge outer housing 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.
6. If there are more than one or two drops of solution remaining in the vial, slowly push the diluent cartridge outer housing cap up until some of the solution is back in the vial and gently tap the click.easy® device. Then draw the solution slowly again back into the cartridge.
7. Remove any excess air that has been drawn into the cartridge by slowly pushing the cap up until no air bubble is visible in the cartridge. There should be no air bubble in the cartridge (Note: Avoid pulling the cap down too fast, as this will draw air into the cartridge).
8. Turn the click.easy® device so that the cap is again on the top. Unscrew the cap and remove it.
9. Remove the cartridge containing the reconstituted SAIZEN solution from the click.easy® device by grasping the end of the cartridge and pulling straight out of the outer housing.
10. Carefully peel off the outer white label on the cartridge using the tab provided by slowly pulling in the direction of the black arrow.



11. Write the reconstitution date on the transparent inner label on the cartridge. This cartridge now contains the reconstituted SAIZEN solution that will be used for your treatment.

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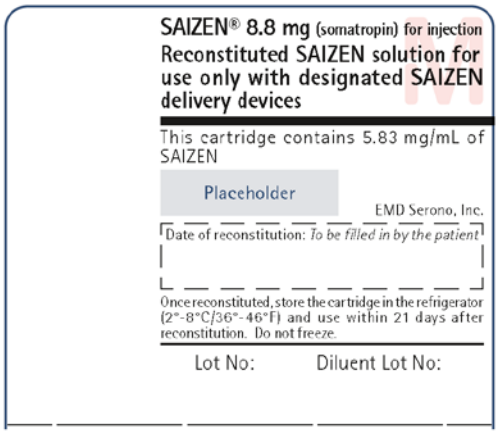

12. The cartridge containing the reconstituted SAIZEN solution is now ready to be used (Note: Please read the instruction manual provided with the injection device for instruction on how to inject the reconstituted SAIZEN solution from the cartridge).
13. The SAIZEN reconstituted solution should be stored in a refrigerator (2°-8°C / 36°-46°F) and should be used within 21 days after reconstitution. Do not freeze.
14. Discard the click.easy® device containing the empty SAIZEN vial safely in accordance with your local requirements. It is not necessary to remove the empty SAIZEN vial from the click.easy® device prior to disposal.
15. Injections should be given in different parts of your body. Do not use any areas in which you feel lumps, firm knots, depressions, or pain; talk to your doctor or healthcare professional about anything you find. Clean the skin at the injection site with soap and water.

STABILITY AND STORAGE

Vials of SAIZEN 8.8 mg pre-assembled in the click.easy® reconstitution device should be stored in the original package at room temperature (15°-30°C / 59°-86°F).

SAIZEN 8.8 mg reconstituted solution should be stored in a refrigerator (2°-8°C / 36°-46°F) and should be used within 21 days after reconstitution.

Do not freeze.

HOW SUPPLIED

SAIZEN 8.8 mg contained in the click.easy® device is available in the following pack sizes:

1 vial of SAIZEN 8.8 mg product and 1 cartridge of 1.51 mL diluent pre-assembled in 1 reconstitution device (click.easy®) comprising 1 device housing and 1 sterile transfer cannula
NDC 44087-1080-1

Manufactured for:
EMD Serono Inc., Rockland, MA 02370