2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been described. In clinical studies with Saizen® involving 280 patients (204 naive and 76 transfer patients), one patient at 6 months of therapy developed anti-GH antibodies with binding capacities exceeding 2 mg/L. Despite the high binding capacity, these antibodies were not growth attenuating. The patient was subsequently shown to have a hGH-N gene defect. Thus, genetic analysis should be undertaken in any patient in whom anti-GH antibodies with high binding capacities occur. No antibodies against proteins of the host cells were detected in the sera of patients treated up to five years.

Any patient with well-documented growth hormone deficiency who fails to respond to therapy should be tested for antibodies to human growth hormone and for thyroid status.

In clinical studies in which Saizen® was administered to growth hormone deficient children, the following events were infrequently seen : local reactions at the injection site (such as pain, numbness, redness and swelling), hypothyroidism, hypoglycemia, seizures, exacerbation of pre-existing psoriasis and disturbances in fluid balance.

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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Saizen® [somatropin (rDNA origin) for injection] dosage and schedule of administration should be individualized for each patient. For the treatment of growth hormone inadequacy, a dosage of 0.06 mg/kg (approximately 0.18 IU/kg) administered 3 times per week by subcutaneous or intramuscular injection is recommended.

Treatment with Saizen® of growth failure due to growth hormone deficiency should be discontinued when the epiphyses are fused. Patients who fail to respond adequately while on Saizen® therapy should be evaluated to determine the cause of unresponsiveness.

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 1-3 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 multi-dose administration. For use in patients sensitive to the diluent, see "WARNINGS".

NEW ▶ NEW ◀

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.** Because Saizen® growth hormone is a protein, shaking can result in a cloudy solution. The Saizen® solution should be clear immediately after reconstitution. **DO NOT INJECT** Saizen® if the reconstituted product is cloudy immediately after reconstitution or refrigeration. Occasionally, after refrigeration, small colorless particles may be present in the Saizen® solution. This is not unusual for proteins like Saizen®.

STABILITY AND STORAGE

Before Reconstitution - Saizen® [somatropin (rDNA origin) for injection] should be stored at room temperature (15°-30°C/59°-86°F). Expiration dates are stated on the labels.

After Reconstitution - When reconstituted with the diluent provided, the reconstituted solution should be stored under refrigeration (2°-8°C/36°-46°F) for up to 14 days. Avoid freezing reconstituted vials of Saizen®.

HOW SUPPLIED

Saizen® [somatropin (rDNA origin) for injection] is a sterile, non-pyrogenic, white, lyophilized powder supplied in packages containing :

1 vial of 5 mg (approximately 15 IU) Saizen® and 1 vial of 10 mL Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1005-2

1 vial of 8.8 mg (approximately 26.4 IU) Saizen® and 1 vial of 10 mL Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1088-1

Rx Only

July, 2002

Manufactured for: Serono Inc., Rockland, MA 02370

® - Registered trademark of Serono inc., Rockland, MA 02370

1005G023
AS2055-12/02

saizen®

[somatropin (rDNA origin) for injection]

For subcutaneous or intramuscular injection

serono

DESCRIPTION

Saizen® [somatropin (rDNA origin) for injection] 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®, with the correct three-dimensional configuration, is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

Saizen® is a highly purified preparation. Biological potency is determined by measuring the increase in body weight induced in hypophysectomized rats.

Saizen® is a sterile, non-pyrogenic, white, lyophilized powder intended for subcutaneous or intramuscular 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.

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

5 mg (approximately 15 IU) vial:

Each vial contains 5.0 mg somatropin (approximately 15 IU), 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 (approximately 26.4 IU) vial:

Each vial contains 8.8 mg somatropin (approximately 26.4 IU), 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

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

CLINICAL PHARMACOLOGY

General

In vitro, preclinical, and clinical testing have demonstrated that Saizen® [somatropin (rDNA origin) for injection] is therapeutically equivalent to pituitary-derived human growth hormone. Clinical studies in normal adults also demonstrated equivalent pharmacokinetics.

Actions that have been demonstrated for Saizen®, somatrem, and/or pituitary-derived human growth hormone include :

A. Tissue Growth-
   1. 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

200

mediators, insulin-like growth factor-I. Serum levels of insulin-like growth factor-I (IGF-I) 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.

2. Cell Growth : Treatment with pituitary-derived human growth hormone results in an increase in both the number and the size of skeletal muscle cells.
3. Organ Growth : Growth hormone of human pituitary origin influences the size and function of internal organs and increases red cell mass. Saizen® has been shown to promote similar organ weight increase to pituitary human growth hormone in an adequate animal model.

B. Protein Metabolism-Linear growth is facilitated in part by growth hormone-stimulated 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 growth hormone therapy.

C. Carbohydrate Metabolism-Growth hormone is a modulator of carbohydrate metabolism. Children with inadequate secretion of growth hormone sometimes experience fasting hypoglycemia that is improved by treatment with growth hormone. 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.

D. Lipid Metabolism-Acute administration of human growth hormone 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 growth hormone administration often decreases body fat. Mean cholesterol levels decreased in patients treated with Saizen®. The clinical significance of this is unknown.

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

F. Connective Tissue/Bone Metabolism-Growth hormone stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Absorption - The absolute bioavailability of recombinant human growth hormone (r-hGH) after subcutaneous administration ranges between 70-90%.

Distribution - The mean volume of distribution of r-hGH given to 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 0.6 hours, whereas subcutaneously and intramuscularly administered somatropin has a half-life of 1.75 and 3.4 hours, respectively. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

Excretion - The mean clearance of intravenously administered r-hGH in six normal male volunteers was 14.6 ± 2.8 L/hr.

Special Populations

Pediatric - The pharmacokinetics of r-hGH is similar in children and adults.

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

Race - No data are available.

Renal Insufficiency - Children and adults with chronic renal failure tend to have decreased clearance of r-hGH as compared to normals.

Hepatic Insufficiency - A reduction in r-hGH clearance has been noted in patients with hepatic dysfunction as compared with normal controls.

INDICATIONS AND USAGE

Saizen® [somatropin (rDNA origin) for injection] is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

CONTRAINDICATIONS

In general, Saizen® [somatropin (rDNA origin) for injection] is contraindicated in the presence of active neoplasia. Any pre-existing neoplasia should be inactive and its treatment complete prior to instituting therapy with Saizen®. Saizen® should be discontinued if there is evidence of recurrent activity. Since, in rare instances, growth hormone deficiency may be an early sign of the presence of a brain tumor, the presence of such a tumor should be ruled out prior to initiation of treatment. Available information suggests that the rate of tumor recurrence is not increased by growth hormone therapy. Saizen® should not be used for growth promotion in pediatric patients with closed epiphyses.

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").

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see "WARNINGS").

WARNINGS

Benzyl Alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. If sensitivity to the diluent occurs, Saizen® [somatropin (rDNA origin) for injection] 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 "CONTRAINDICATIONS" for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone 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 growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General : Saizen® [somatropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of growth disorders.

Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Human growth hormone should be used with caution in patients with diabetes mellitus or a family history of diabetes mellitus.

Hypothyroidism may develop during Saizen® therapy. Untreated hypothyroidism will jeopardize the response to growth hormone. Therefore, thyroid hormone determinations should be performed periodically during Saizen® administration and thyroid hormone replacement should be initiated when indicated.

Bone age should be monitored periodically during Saizen® administration especially in patients who are pubertal and/or receiving concomitant thyroid replacement therapy. Under these circumstances, epiphyseal maturation may progress rapidly.

Patients with endocrine disorders, including growth hormone deficiency, may have an increased incidence of slipped capital femoral epiphysis. Any child who develops a limp or complains of hip or knee pain during growth hormone therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products and it also has been associated more commonly with IGF-I. Symptoms usually occurred within the first eight weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after temporary suspension or termination of therapy. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

When growth hormone 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.

As for any protein, local or systemic allergic reactions may occur. Parents/Patient should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Laboratory Tests : Serum levels of inorganic phosphorus, alkaline phosphatase, and IGF-I may increase with Saizen® therapy.

Drug Interaction : Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Saizen®. There was no evidence in the controlled studies of Saizen® interaction with drugs commonly used in the treatment of routine pediatric problems/illnesses. However, formal drug interaction studies have not been conducted.

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.

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.

Nursing Women : 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.

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 may be more prone to develop adverse reactions.

Information For Patients : Patients being treated with growth hormone and/or their parents should be informed of the potential benefits and risks associated with treatment. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including a review of the contents of the Patient Information Insert. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

If home use is prescribed, a puncture resistant container for the disposal of used syringes and needles should be recommended to the patient. Patients and/or parents should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes (see Patient Information Insert).

ADVERSE REACTIONS

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Anti-growth hormone (GH) antibody capacities below

EDP-1543 Noir EDP-1543 072 EDP-1543 194
EDP-1543 3025 EDP-1543 306

NDC 44087-1005-2

saizen® mg

[somatropin (rDNA origin) for injection]

5 mg (approximately 15 IU)

Rx Only

- 1 vial somatropin (rDNA origin) for injection
- 1 vial Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol)
- For subcutaneous or intramuscular injection.

serono

USA

Lot No.:

Exp. Date:

Reconstitute each 5 mg vial in 1 - 3 mL Bacteriostatic Water for Injection,USP (0.9 % Benzyl Alcohol). Approximately 10% mechanical loss can be associated with reconstitution and multi-dose administration.
Storage : Room Temperature (15°-30°C/ 59°-86°F).
Reconstituted vials should be refrigerated and used within 14 days.
Usual Dosage : See package insert.
Multiple dose vial

s.c./i.m.

NEW

NDC 44087-1005-2

saizen® mg

[somatropin (rDNA origin) for injection]

5 mg (approximately 15 IU)

Rx Only

- 1 vial somatropin (rDNA origin) for injection
- 1 vial Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol)
- For subcutaneous or intramuscular injection.

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Contents :
One vial Saizen® containing 5 mg somatropin (approximately 15 IU), 34.2 mg sucrose, 1.165 mg O-phosphoric acid and sodium hydroxide or O-phosphoric acid to adjust pH.
One vial Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) containing 10 mL.

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

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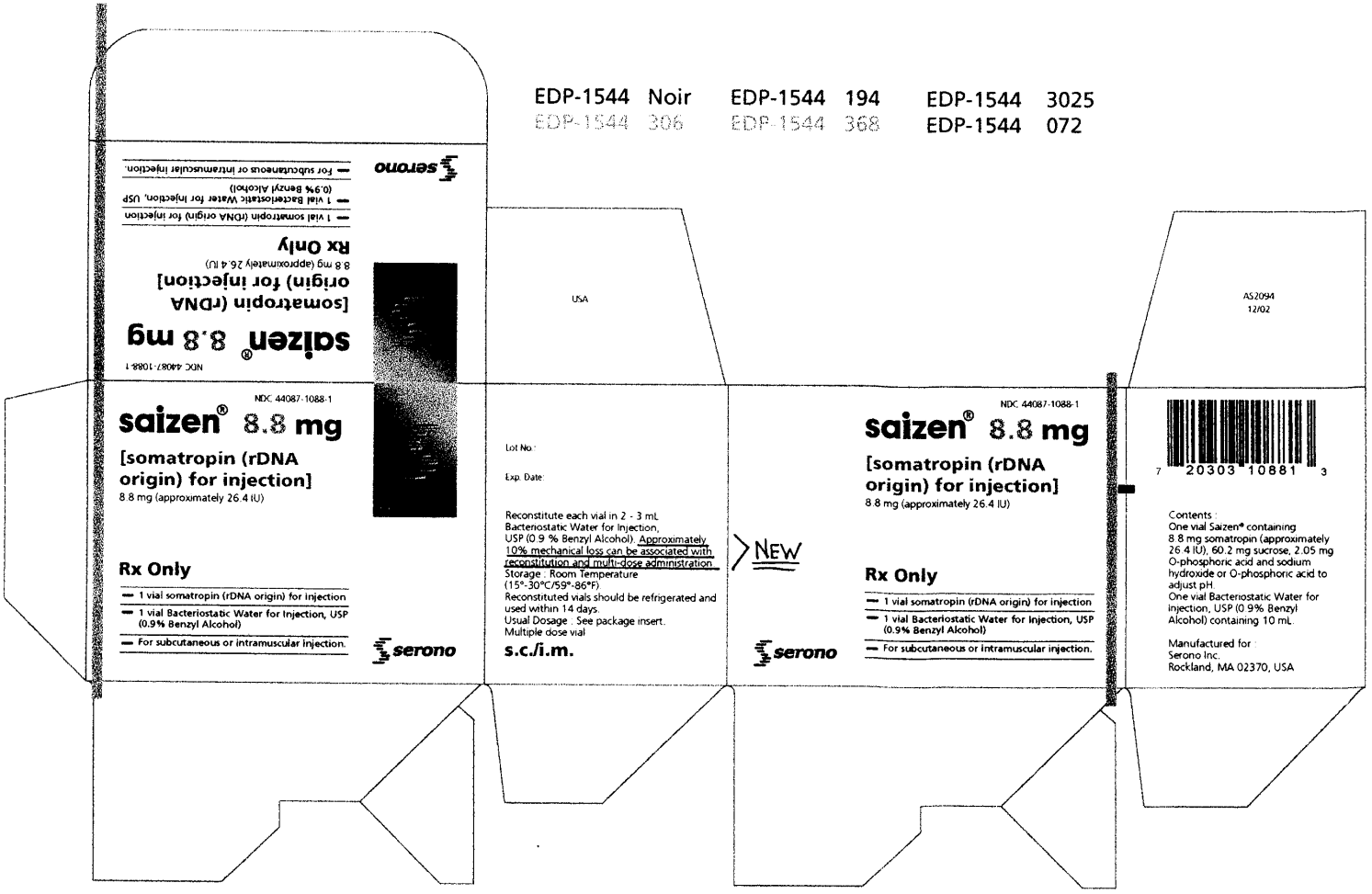
EDP-1544 Noir EDP-1544 194 EDP-1544 3025
EDP-1544 306 EDP-1544 368 EDP-1544 072



NDC 44087-1088-1

saizen® 8.8 mg

[somatropin (rDNA origin) for injection]

8.8 mg (approximately 26.4 IU)

Rx Only

- 1 vial somatropin (rDNA origin) for injection
- 1 vial Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol)
- For subcutaneous or intramuscular injection.

serono

NDC 44087-1088-1

saizen® 8.8 mg

[somatropin (rDNA origin) for injection]

8.8 mg (approximately 26.4 IU)

Rx Only

- 1 vial somatropin (rDNA origin) for injection
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- For subcutaneous or intramuscular injection.

serono

- 1 vial somatropin (rDNA origin) for injection
- 1 vial Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol)
- For subcutaneous or intramuscular injection.

serono

USA

Lot No.:

Exp. Date:

Reconstitute each vial in 2 - 3 mL Bacteriostatic Water for Injection, USP (0.9 % Benzyl Alcohol). Approximately 10% mechanical loss can be associated with reconstitution and multi-dose administration.
Storage : Room Temperature (15°-30°C/59°-86°F).
Reconstituted vials should be refrigerated and used within 14 days.
Usual Dosage : See package insert.
Multiple dose vial

s.c./i.m.

NEW

AS2094
12/02

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Contents :
One vial Saizen® containing 8.8 mg somatropin (approximately 26.4 IU), 60.2 mg sucrose, 2.05 mg O-phosphoric acid and sodium hydroxide or O-phosphoric acid to adjust pH.
One vial Bacteriostatic Water for injection, USP (0.9% Benzyl Alcohol) containing 10 mL.

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

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