



CALCITONIN SALMON Injection, USP, Synthetic

3003663A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALCITONIN SALMON INJECTION safely and effectively. See full prescribing information for CALCITONIN SALMON INJECTION.

CALCITONIN SALMON injection, synthetic, for subcutaneous or intramuscular use

Initial U.S. Approval: 1975

INDICATIONS AND USAGE

Calcitonin salmon injection, synthetic, is a calcitonin, indicated for the following conditions:

- Treatment of symptomatic Paget's disease of bone when alternative treatments are not suitable (1.1)
- Treatment of hypercalcemia (1.2)
- Treatment of postmenopausal osteoporosis when alternative treatments are not suitable. Fracture reduction efficacy has not been demonstrated (1.3)

Limitations of Use:

- Due to the possible association between malignancy and calcitonin salmon use, the need for continued therapy should be re-evaluated on a periodic basis (1.4, 5.3)

DOSAGE AND ADMINISTRATION

- Symptomatic Paget's disease of bone: 100 International Units daily. Ensure adequate calcium and vitamin D intake (2.1, 2.5)
- Hypercalcemia: start with 4 International Units/kg body weight every 12 hours. Increase to 8 International Units/kg every 12 hours if no improvement in 1 to 2 days. Increase further to 8 International Units/kg every 6 hours if no improvement after 2 more days (2.2)
- Postmenopausal osteoporosis: 100 International Units daily. Ensure adequate calcium and vitamin D intake (2.3, 2.5)

DOSAGE FORMS AND STRENGTHS

- Injection: 200 International Units per mL sterile solution in 2 mL multi-dose vials (3)

CONTRAINDICATIONS

Hypersensitivity to calcitonin salmon or any of the excipients (4)

WARNINGS AND PRECAUTIONS

- Serious hypersensitivity reactions, including reports of fatal anaphylaxis have been reported. Consider skin testing prior to treatment in patients with suspected hypersensitivity to calcitonin salmon (5.1)
- Hypocalcemia has been reported. Ensure adequate intake of calcium and vitamin D (5.2)
- Malignancy: A meta-analysis of 21 clinical trials suggests an increased risk of overall malignancies in calcitonin salmon-treated patients (5.3, 6.1)
- Circulating antibodies to calcitonin salmon may develop, and may cause loss of response to treatment (5.4)

ADVERSE REACTIONS

Most common adverse reactions are nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2% to 5%) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of calcitonin salmon and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may require adjustment (7)

USE IN SPECIFIC POPULATIONS

There are no data to support use in children (8.4)

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION:

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Paget's Disease of Bone

Calcitonin salmon injection is indicated for the treatment of symptomatic Paget's disease of bone in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion. There is no evidence that the prophylactic use of calcitonin salmon is beneficial in asymptomatic patients. Calcitonin salmon injection should be used only in patients who do not respond to alternative treatments or for whom such treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).

1.2 Treatment of Hypercalcemia

Calcitonin salmon injection is indicated for the early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents.

1.3 Treatment of Postmenopausal Osteoporosis

Calcitonin salmon injection is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause. The evidence of efficacy for calcitonin salmon injection is based on increases in total body calcium observed in clinical trials. Fracture reduction efficacy has not been demonstrated. Calcitonin salmon injection should be reserved for

patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).

1.4 Important Limitations of Use

Due to the possible association between malignancy and calcitonin salmon use, the need for continued therapy should be re-evaluated on a periodic basis [see *Warnings and Precautions* (5.3)].

2 DOSAGE AND ADMINISTRATION

2.1 Paget's Disease of Bone

The recommended dose of calcitonin salmon injection for treatment of symptomatic Paget's disease of bone is 100 International Units (0.5 mL) per day administered subcutaneously or intramuscularly.

2.2 Hypercalcemia

The recommended starting dose of calcitonin salmon injection for early treatment of hypercalcemia is 4 International Units/kg body weight every 12 hours by subcutaneous or intramuscular injection. If the response to this dose is not satisfactory after one or two days, the dose may be increased to 8 International Units/kg every 12 hours. If the response remains unsatisfactory after two more days, the dose may be further increased to a maximum of 8 International Units/kg every 6 hours.

2.3 Postmenopausal Osteoporosis

The recommended dose of calcitonin salmon injection for treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause is 100 International Units (0.5 mL) per day administered subcutaneously or intramuscularly. The minimum effective dose of calcitonin salmon injection for the prevention of vertebral bone mineral density loss has not been established.

2.4 Preparation and Administration

Visually inspect calcitonin salmon injection vials. Calcitonin salmon injection is a clear, colorless, solution. If the solution is not clear and colorless, or contains any particles, or if the vial is damaged, do not administer the solution.

If the volume of calcitonin salmon injection to be injected exceeds 2 mL, intramuscular injection is preferable and the total dose should be distributed across multiple sites of injection.

Instruct patients to use sterile injection technique when administering calcitonin salmon injection, and to dispose of needles properly.

2.5 Recommendations for Calcium and Vitamin D Supplementation

Patients who use calcitonin salmon injection for treatment of postmenopausal osteoporosis should receive adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (at least 400 International Units per day).

3 DOSAGE FORMS AND STRENGTHS

Calcitonin Salmon Injection, USP, Synthetic is available as a clear, colorless, sterile solution of synthetic calcitonin salmon in individual 2 mL multi-dose vials containing 200 International Units per mL.

4 CONTRAINDICATIONS

Hypersensitivity to calcitonin salmon or any of the excipients. Reactions have included anaphylaxis with death, bronchospasm, and swelling of the tongue or throat [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported in patients receiving calcitonin salmon injection, e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock, and death due to anaphylaxis. Appropriate medical support and monitoring measures should be readily available when calcitonin salmon injection is administered. If anaphylaxis or other severe hypersensitivity/allergic reactions occur, initiate appropriate treatment [see *Contraindications* (4)].

For patients with suspected hypersensitivity to calcitonin salmon, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of calcitonin salmon injection. Healthcare providers may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Information Department of Par Pharmaceutical.

5.2 Hypocalcemia

Hypocalcemia associated with tetany (i.e., muscle cramps, twitching) and seizure activity has been reported with calcitonin salmon injection therapy. Hypocalcemia must be corrected before initiating therapy. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients at risk for hypocalcemia, provisions for parenteral calcium administration should be available during the first several administrations of calcitonin salmon and serum calcium and symptoms of hypocalcemia should be monitored. Use of calcitonin salmon injection for the treatment of Paget's disease or postmenopausal osteoporosis is recommended in conjunction with an adequate intake of calcium and vitamin D [see *Dosage and Administration* (2.5)].

5.3 Malignancy

In a meta-analysis of 21 randomized, controlled clinical trials with calcitonin salmon (nasal spray or investigational oral formulations), the overall incidence of malignancies reported was higher among calcitonin salmon-treated patients (4.1%) compared with placebo-treated patients (2.9%). This suggests an increased risk of malignancies in calcitonin salmon-treated patients compared to placebo-treated patients. It is not possible to exclude an increased risk when calcitonin salmon is administered long-term subcutaneously, intramuscularly, or intravenously. The benefits for the individual patient should be carefully considered against possible risks [see *Adverse Reactions* (6.1)].

5.4 Antibody Formation

Circulating antibodies to calcitonin salmon have been reported with calcitonin salmon injection. The possibility of antibody formation should be considered in any patient with an initial response to calcitonin salmon injection who later stops responding to treatment [see *Adverse Reactions* (6.3)].

5.5 Urine Sediment Abnormalities

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the urine sediment normalized after calcitonin salmon was stopped. Periodic examinations of urine sediment should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Hypersensitivity Reactions, including anaphylaxis [see *Warnings and Precautions* (5.1)]
- Hypocalcemia [see *Warnings and Precautions* (5.2)]
- Malignancy [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of calcitonin salmon injection was assessed in open-label trials several months to two years in duration. The most common adverse reactions are discussed below.

Nausea: Nausea with or without vomiting has been noted in about 10% of patients treated with calcitonin salmon. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration.

Dermatologic Reactions: Local inflammatory reactions at the site of subcutaneous or intramuscular injection have been reported in about 10% of patients. Flushing of face or hands occurred in about 2% to 5% of patients. Skin rashes and pruritus of the ear lobes have also been reported.

Other Adverse Reactions: Nocturia, feverish sensation, pain in the eyes, poor appetite, abdominal pain, pedal edema, and salty taste have been reported in patients treated with calcitonin salmon injection.

Malignancy

A meta-analysis of 21 randomized, controlled clinical trials with calcitonin salmon (nasal spray or investigational oral formulations) was conducted to assess the risk of malignancies in calcitonin salmon-treated patients compared to placebo-treated patients. The trials in the meta-analysis ranged in duration from 6 months to 5 years and included a total of 10883 patients (6151 treated with calcitonin salmon and 4732 treated with placebo). The overall incidence of malignancies reported in these 21 trials was higher among calcitonin salmon-treated patients (254/6151 or 4.1%) compared with placebo-treated patients (137/4732 or 2.9%). Findings were similar when analyses were restricted to the 18 nasal spray only trials [calcitonin salmon 122/2712 (4.5%); placebo 30/1309 (2.3%)].

The meta-analysis results suggest an increased risk of overall malignancies in calcitonin salmon-treated patients compared to placebo-treated patients when all 21 trials are included and when the analysis is restricted to the 18 nasal spray only trials (see *Table 1*). It is not possible to exclude an increased risk when calcitonin salmon is administered by the subcutaneous, intramuscular, or intravenous route because these routes of administration were not investigated in the meta-analysis. The increased malignancy risk seen with the meta-analysis was heavily influenced by a single large 5-year trial, which had an observed risk difference of 3.4% [95% CI (0.4%, 6.5%)]. Imbalances in risks were still observed when analyses excluded basal cell carcinoma (see *Table 1*); the data were not sufficient for further analyses by type of malignancy. A mechanism for these observations has not been identified. Although a definitive causal relationship between calcitonin salmon use and malignancies cannot be established from this meta-analysis, the benefits for the individual patient should be carefully evaluated against all possible risks [see *Warnings and Precautions* (5.3)].

