

4. Carcinogenicity, Mutagenicity, Impairment of Fertility

An increased incidence of non-functioning pituitary adenomas has been observed in 1-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 International Units per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area).

The findings suggest that calcitonin-salmon reduced the latency period for development of the pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon was tested for mutagenicity using four strains of *Salmonella typhimurium* and two strains of *Escherichia coli*, with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in Chinese Hamster ovary cells *in vitro*.

5. Laboratory Tests

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin-salmon nasal spray. Coarse granular 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 evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered.

6. Pregnancy

Teratogenic Effects

Category C.

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women with calcitonin-salmon. FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is not indicated for use in pregnancy.

7. Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

8. Pediatric Use

There are no data to support the use of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is limited.

9. Geriatric Use

In a large multi-centered, double-blind, randomized clinical study of calcitonin-salmon nasal spray, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old and 196 patients were 75 and over. Compared to subjects less than 65 years old, the incidence of nasal adverse events (rhinitis, irritation, erythema, and excoriation) was higher in patients over the age of 65, particularly those over the age of 75. Most events were mild in intensity. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to calcitonin-salmon nasal spray (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of calcitonin-salmon nasal spray treated patients are presented in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

Adverse Reaction	Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically	
	Calcitonin-Salmon	
	Nasal Spray N=341 % of Patients	Placebo N=131 % of Patients
Rhinitis	12.0	6.9
Symptom of Nose†	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with calcitonin-salmon nasal spray. Adverse events reported in 1%-3% of patients are identified with an asterisk(*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to calcitonin-salmon nasal spray has not been established.

Body as a whole – General Disorders: influenza-like symptoms*, fatigue*, periorbital edema, fever

Integumentary: erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, parosmia

Cardiovascular: hypertension*, angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction

Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, flatulence, increased appetite, gastritis, dry mouth

Liver/Metabolic: cholelithiasis, hepatitis, thirst, weight increase

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation

Hearing/Vestibular: tinnitus, hearing loss, earache

Vision: abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater

Vascular: flushing, cerebrovascular accident, thrombophlebitis

Hematologic/Resistance Mechanisms: lymphadenopathy*, infection*, anemia

Psychiatric: depression*, insomnia, anxiety, anorexia

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with calcitonin-salmon nasal spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3%-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with calcitonin-salmon nasal spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE

No instances of overdose with calcitonin-salmon nasal spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of calcitonin-salmon nasal spray up to 1600 International Units, doses up to 800 International Units per day for 3 days and chronic administration of doses up to 600 International Units per day have been studied without serious adverse effects. A 1000 International Units dose of calcitonin-salmon injectable product given subcutaneously may produce nausea and vomiting. A 32 International Units per kg per day dose of calcitonin-salmon injectable product for 1 or 2 days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray in postmenopausal osteoporotic patients is 1 spray (200 International Units) per day administered intranasally, alternating nostrils daily. Each bottle, filled with 3.7 mL of solution, contains enough medication for 30 doses. Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of calcitonin-salmon nasal spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to calcitonin-salmon nasal spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, allow the bottle to reach room temperature. Remove the protective cap and clip from the bottle of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray. To prime the pump, hold the bottle upright and depress the two white side arms of the pump toward the bottle at least 5 times until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position and the pump firmly depressed toward the bottle. The pump should NOT be primed before each daily use.

HOW SUPPLIED

FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is presented as a metered dose solution in a 3.7 mL fill amber glass bottle. It is available in a dosage strength of 200 International Units per activation (0.09 mL). A screw-on pump is provided. Following priming, the pump will deliver solution containing 200 International Units of calcitonin-salmon per activation. FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray contains 2200 International Units/mL calcitonin-salmon and is provided in individual boxes containing one glass bottle with screw cap and one screw-on pump (NDC# 0245-0008-35).

Store and Dispense

Store unopened bottle in refrigerator between 36-46°F (2-8°C). **Protect from freezing.** After opening, store bottle in use in an upright position for up to 30 days at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] **Discard 30 days after first use.**

Distributed by

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US Patent 6,440,392

US Patent 6,103,495

US Patent 6,210,925

US Patent 6,627,438

US Patent 6,737,250

US Patent 5,789,234

FCPI02

Revised 0606