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FORTICAL®

calcitonin-salmon

(rDNA origin)

Nasal Spray

For Intranasal Use Only

Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

The active ingredient in FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is a polypeptide of 32 amino acids manufactured by recombinant DNA technology and is identical to calcitonin-salmon produced by chemical synthesis.

This is shown by the following graphic formula:

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H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
 1   2   3   4   5   6   7   8   9   10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
11  12  13  14  15  16  17  18  19  20

Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
21  22  23  24  25  26  27  28  29  30

Thr-Pro-NH2
31  32
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It is provided in a 3.7 mL fill glass bottle as a solution for intranasal administration with sufficient medication for at least 30 doses. Each spray delivers 200 International Units calcitonin-salmon in a volume of 0.09 mL.

Active Ingredient: Calcitonin-salmon 2200 International Units/mL, corresponding to 200 International Units per actuation (0.09 mL).

Inactive Ingredients: Sodium chloride USP, Citric Acid USP, Phenylethyl Alcohol USP, Benzyl Alcohol NF, Polysorbate 80 NF, Hydrochloric Acid NF or Sodium Hydroxide NF (added as necessary to adjust pH) and Purified Water USP.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with *injectable* calcitonin. The mean bioavailability of calcitonin-salmon nasal spray is approximately 3% of the injectable calcitonin in normal subjects and, therefore, the conclusions concerning the CLINICAL PHARMACOLOGY of this preparation may be different.

The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts.

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon

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causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium towards the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium in the limits of the normal range. In normal children and in patients with Paget's disease in whom bone resorption is more rapid, decreases in serum calcium are more pronounced in response to calcitonin.

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in the formation of normal bone.

***Postmenopausal Osteoporosis*:** Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal women. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation, which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fracture). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Calcitonin, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

***Calcium Homeostasis*:** In two clinical studies designed to evaluate the pharmacodynamic

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response to calcitonin-salmon nasal spray, administration of 100-1600 International Units to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 International Units did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal women.

***Kidney*:** Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been conducted with FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

Gastrointestinal Tract: Some evidence from studies with injectable preparations suggests that calcitonin may have significant actions on the gastrointestinal tract. Short-term administration of injectable calcitonin results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated. These studies have not been conducted with FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

Pharmacokinetics and Drug Metabolism

The pharmacokinetic properties of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray after multiple dose administration were shown to be similar to that of a commercially available calcitonin-salmon product in healthy volunteers. The data on bioavailability of calcitonin-salmon nasal spray obtained by various investigators using different methods show great variability. FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is absorbed rapidly by the nasal mucosa. In normal volunteers approximately 3% (range 0.3%-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by intramuscular injection. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of nasally administered calcitonin has not been studied in postmenopausal women.

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INDICATIONS AND USAGE

Postmenopausal Osteoporosis – FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women. Use of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and Vitamin D (400 International Units per day) intake to retard the progressive loss of bone mass. The evidence of efficacy for calcitonin-salmon is based on increases in spinal bone mineral density (BMD) observed in clinical trials.

Two randomized, placebo-controlled trials were conducted in 325 postmenopausal women (227 treated with calcitonin-salmon nasal spray and 98 treated with placebo) with spinal, forearm or femoral BMD at least one standard deviation below the normal value for healthy premenopausal women. These studies conducted over two years demonstrated that 200 International Units daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic women who were greater than 5 years postmenopause. Calcitonin-salmon nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as 6 months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 1 year of treatment changing to a trend at 2 years that was no longer statistically significant.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

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Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of allergic-type reactions have been reported in patients receiving calcitonin-salmon nasal spray, including one case of anaphylactic shock, which appears to have been due to the preservative because the patient could tolerate injectable calcitonin-salmon without incident. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g. bronchcospasm, swelling of the tongue or throat, anaphylactic shock, and in one case death attributed to anaphylaxis). The usual provisions should be made for emergency treatment if such a reaction should occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of a calcitonin-salmon injectable product. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from Upsher-Smith Laboratories, Inc. by calling toll-free at 1-800-654-2299.

PRECAUTIONS

1. Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done.

Currently, no drug interactions with calcitonin-salmon have been observed. The effects of prior use of diphosphonates in postmenopausal osteoporosis patients have not been assessed; however, in patients with Paget's disease prior diphosphonate use appears to reduce the anti-resorptive response to calcitonin-salmon nasal spray.

2. Periodic Nasal Examinations

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

The development of mucosal alterations or transient nasal conditions have been reported in up to 9% of patients who received calcitonin-salmon nasal spray and in up to 12% of patients who

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received placebo nasal spray in studies in postmenopausal women. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

In all postmenopausal patients treated with calcitonin-salmon nasal spray, the most commonly reported nasal adverse events included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. One patient (0.3%) treated with calcitonin-salmon nasal spray who was receiving 400 International Units daily developed a small nasal wound. In clinical trials in another disorder (Paget's disease), 2.8% of patients developed nasal ulcerations.

If severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5mm in diameter or penetrating below the mucosa, or those associated with heavy bleeding, calcitonin-salmon nasal spray should be discontinued. Although smaller ulcers often heal without withdrawal of calcitonin-salmon nasal spray, medication should be discontinued temporarily until healing occurs.

3. Information for Patients

Careful instructions on pump assembly, priming of the pump and nasal introduction of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray should be given to the patient. Although instructions for patients are supplied with the individual bottle, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 36-46°F (2^{-}8°C).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- After opening, store bottle in use with pump attached at room temperature in an upright position, for up to 30 days. Each bottle contains sufficient medication for 30 doses.
- Discard 30 days after first use.

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- See **DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump** for complete instructions on priming the pump and administering FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

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.

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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. Geriatric Use

Clinical trials using calcitonin-salmon nasal spray have included postmenopausal patients up to 77 years of age. No unusual adverse events or increased incidence of common adverse events have been noted in patients over 65 years of age.

9. Pediatric Use

There are no data to support the use of FORTICAL® calcitonin-salmon (rDNA origin) **N**asal 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.

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

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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 Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically

Adverse Reaction	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

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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

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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 Unit 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.

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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.**

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US Patent 6,440,392

US Patent 6,103,495

US Patent 6,210,925

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