

**Capsitonin<sup>®</sup>**  
**(calcitonin-salmon)**

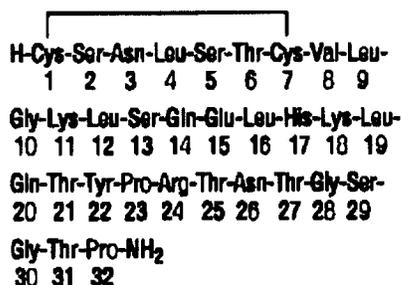
**Capsules**

**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.

Capsitonin<sup>®</sup> (calcitonin-salmon) is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in a 28 day calendar pack.

*Active Ingredient:* calcitonin-salmon 2500 I.U. per capsule.

*Inactive Ingredients:* chenodeoxycholic acid and propyl gallate.

The activity of Capsitonin<sup>®</sup> is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control, Holly Hill, London.

**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 Capsitonin<sup>®</sup> (calcitonin-salmon)

is approximately X%. In clinical studies a dose of YY oral calcitonin formulated as Capsitonin<sup>®</sup> has been shown to be equivalent to 200 IU of intranasal calcitonin.

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 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 the *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 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 females. 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' fractures). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Calcitonin-salmon, 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 a clinical study of XX subjects a dose of XX oral calcitonin has been shown to be equivalent to 200 I.U. of nasal calcitonin. Serum levels of C terminal peptide were identical in the populations studied. On this basis Capsitonin<sup>®</sup> is considered equivalent in effect to the current nasal formulations. No clinical studies of Capsitonin<sup>®</sup> have been performed looking at changes in bone mineral density. Evidence of the effects of Capsitonin<sup>®</sup> is inferred from the use of the nasal formulation.

In two clinical studies designed to evaluate the pharmacodynamic response to calcitonin-salmon nasal spray, administration of 100-1600 I.U. 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 I.U. 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 females.

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*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 carried out with Capsitonin®.

*Gastrointestinal Tract* - Some evidence from studies with injectable preparations suggest 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 Capsitonin®.

**Pharmacokinetics and Metabolism**

The data on bioavailability of Capsitonin® oral calcitonin obtained by various investigators using different methods show great variability. Peak plasma concentrations of drug appear 31-39 minutes after oral administration compared to 16-25 minutes following parenteral dosing. In osteoporotic women approximately X% (range TBD) of an orally administered dose is bioavailable compared to the same dose administered by intramuscular injection.

**INDICATION AND USAGE**

*Postmenopausal Osteoporosis* - Capsitonin® (calcitonin-salmon) is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Capsitonin® should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of Capsitonin® is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 I.U. per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

A single randomized, cross over controlled trial was conducted in XXX postmenopausal females. This trial demonstrated that Capsitonin® at a dose of YY per day lead to identical changes in C terminal peptide levels. A dose of XX Capsitonin® is therefore equivalent to 200 iu of intranasal calcitonin.

**CONTRAINDICATIONS**

Clinical allergy to calcitonin-salmon.

**WARNINGS**

**Allergic Reactions**

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., bronchospasm, swelling of the tongue or throat, anaphylactic shock, and in one case death attributed to anaphylaxis). The usual provisions should be made

for the emergency treatment of such a reaction should it 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 calcitonin-salmon injection. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

## **PRECAUTIONS**

### **1. Drug Interactions**

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Capsitonin<sup>®</sup> (calcitonin-salmon) ingredients.

### **2. Information for Patients**

Capsitonin<sup>®</sup> tablets should be stored at room temperature away from sunlight.

### **3. Carcinogenicity, Mutagenicity, and Impairment of Fertility**

An increased incidence of non-functioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 LV. 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 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 *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), 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 mammalian V79 cells of the Chinese Hamster *in vitro*.

### **4. 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. Capsitonin® 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 Capsitonin® 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 very limited.

## **ADVERSE REACTIONS**

The information below, describing the adverse reactions of calcitonin, has been derived from studies with *nasal* calcitonin.

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 below 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).

In addition, the events were reported in

Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically		
Adverse Reaction	Miacalcin® (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.

following adverse events were reported in fewer than 3% of

Division of Dockets Management

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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 Capsitonin<sup>®</sup> 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.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of calcitonin-salmon 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 Capsitonin<sup>®</sup> (calcitonin-salmon) in postmenopausal osteoporotic females is one capsule per day.

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 Capsitonin<sup>®</sup> therapy in these patients.

## **HOW SUPPLIED**

### **Capsitonin<sup>®</sup> (calcitonin-salmon)**

Available as a capsule. It is available in a dosage strength of 2500 I.U. per capsule. Capsitonin<sup>®</sup> contains 2500 I.U. calcitonin-salmon and is provided in an individual box containing 28 capsules.

### ***Store and Dispense***

Store box at room temperature between 15°C-30°C (59°F-86°F) in an upright position. Each box contains 28 doses.



**Bone Medical**

Manufactured by:  
TBD

Distributed by:  
TBD.