CALCITONIN SALMON - calcitonin salmon spray, metered
Physicians Total Care, Inc.

Calcitonin-Salmon
Nasal Spray, USP
Rx Only
Prescribing Information

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.

Calcitonin-Salmon Nasal Spray 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 3.7 mL fill glass bottles as a solution for nasal administration. This is sufficient medication for at least 30 doses.

*Active Ingredient:*calcitonin-salmon, 2200 I.U. per mL (corresponding to 200 I.U. per 0.09 mL actuation).

*Inactive Ingredients:*sodium chloride, chlorobutanol, hydrochloric acid (added as necessary to adjust pH), purified water and nitrogen.

The activity of Calcitonin-Salmon Nasal Spray 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 Calcitonin-Salmon Nasal Spray is approximately 3% of that of 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 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 Nasal Spray, given by the intranasal route, has been shown to increase spinal bone mass in post-menopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis

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.

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 Calcitonin-Salmon Nasal Spray.

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 Calcitonin-Salmon Nasal Spray.

Pharmacokinetics and Metabolism

The bioavailability of Calcitonin-Salmon Nasal Spray relative to intramuscular administration is between 3 and 5%. Calcitonin-Salmon Nasal Spray is absorbed by the nasal mucosa with a mean T_{max} of about 13 minutes. The terminal half-life of calcitonin-salmon has been calculated to be around 18 minutes and no evidence of accumulation was observed with multiple dosing. Plasma exposure was higher following administration of 400 IU nasal spray compared to that after 200 IU dose. As is the case with other polypeptide hormones, there is very little value in monitoring plasma levels of salmon calcitonin since these are not directly predictive of the therapeutic response. Hence, Calcitonin-Salmon activity should be evaluated by using clinical parameters of efficacy.

INDICATIONS AND USAGE

Postmenopausal Osteoporosis

Calcitonin-Salmon Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Calcitonin-Salmon Nasal Spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of Calcitonin-Salmon Nasal Spray 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.

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females [227 Calcitonin-Salmon Nasal Spray treated and 98 placebo treated] with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 I.U. daily of Calcitonin-Salmon Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females 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

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of serious allergic-type reactions have been reported in patients receiving Calcitonin-Salmon Nasal Spray, including cases of anaphylaxis and anaphylactic shock. 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), including very rare reports of 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 Drug Safety Department of Par Pharmaceutical Companies Inc. at 1-800-828-9393.

PRECAUTIONS

Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Calcitonin-Salmon Nasal Spray ingredients.

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

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.

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 occurred in up to 9% of patients who received Calcitonin-Salmon Nasal Spray and in up to 12% of patients who received placebo nasal spray in studies in postmenopausal females. 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 I.U. 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 1.5 mm 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.

Information for Patients

Careful instructions on pump assembly, priming of the pump and nasal introduction of Calcitonin-Salmon Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, 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 2°C-8°C (36°F-46°F).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- Store bottle in use at room temperature 20°C to 25°C (68°F to 77°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.
- See DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump for complete instructions on priming the pump and administering Calcitonin-Salmon Nasal Spray.

You should keep track of the number of doses used from the bottle.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Carcinogenicity and 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 I.U. 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*.

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.

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. Calcitonin-Salmon Nasal Spray is *not* indicated for use in pregnancy.

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.

Pediatric Use

There are no data to support the use of Calcitonin-Salmon 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 very limited.

Geriatric Use

In one 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 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).

Adverse Reactions Occurring in at Least 3% Of Postmenopausal Patients Treated Chronically

Calcitonin-Salmon		
	Nasal SprayN = 341	PlaceboN = 131
Adverse Reaction	**% of Patients**	**% 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.

Body as a whole – General Disorders: influenza-like symptoms*, fatigue*, edema (facial, peripheral and generalized), 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, nasal congestion, sneezing, allergic rhinitis, nasal odor, mucosal excoriation, rhinitis ulcerative

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, visual disturbance

Vascular: flushing, cerebrovascular accident, thrombophlebitis

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

Psychiatric: depression*, insomnia, anxiety, anorexia

Immune system disorders: Hypersensitivity, anaphylaxis and anaphylactic shock

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 I.U., doses up to 800 I.U. per day for 3 days and chronic administration of doses up to 600 I.U. per day have been studied without serious adverse effects. A dose of 1000 I.U. of Calcitonin-Salmon injectable solution given subcutaneously may produce nausea and vomiting. A dose of Calcitonin-Salmon injectable solution of 32 I.U. per kg per day for 1 or 2 days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of Calcitonin-Salmon 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 Calcitonin-Salmon Nasal Spray in postmenopausal osteoporotic females is one spray (200 I.U.) per day administered intranasally, alternating nostrils daily.

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, Calcitonin-Salmon Nasal Spray should be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle 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 dose.

HOW SUPPLIED

Calcitonin-Salmon Nasal Spray, USP

Available as a metered dose clear solution in a 3.7 mL fill clear glass bottle. It is available in a dosage strength of 200 I.U. per activation (0.09 mL/spray). A screw-on pump is provided. The pump, following priming, will deliver 0.09 mL of solution. Calcitonin-Salmon Nasal Spray contains 2200 I.U./mL calcitonin-salmon and is provided in an individual box containing one glass bottle and one screw-on pump (NDC 54868-6323-0).

Store and Dispense

Store unopened bottle in refrigerator between 2°C-8°C (36°F-46°F). Protect from freezing.

Store bottle in use at room temperature between 20°C-25°C (68°F-77°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

INFORMATION FOR THE PATIENT

Calcitonin-Salmon Nasal Spray, USP

What is CALCITONIN-SALMON Nasal Spray?

CALCITONIN-SALMON Nasal Spray is a medication used for the treatment of osteoporosis after menopause (postmenopausal osteoporosis) in women more than 5 years after menopause with low bone mass who refuse or cannot tolerate estrogens, or in whom estrogens are not an option. Patients who use CALCITONIN-SALMON Nasal Spray should be sure to ingest adequate amounts of calcium and vitamin D along with therapy.

How much calcium and vitamin D do I need each day?

When taking CALCITONIN-SALMON Nasal Spray, it is recommended that you get at least 1000 mg of calcium and 400 I.U. (international units) of vitamin D each day. Check with your doctor or healthcare provider to see if you are getting enough calcium and vitamin D in your diet. If not, he or she may recommend that you start taking calcium and vitamin D supplements.

What is osteoporosis after menopause? What causes it?

Postmenopausal osteoporosis is a condition associated with frail, brittle bones. It usually occurs when "old" bone cells are removed from bones faster than they can be replaced by "new" bone cells. As a result, bones get weak and may become susceptible to fractures.

Osteoporosis occurs most frequently in women who have gone through menopause. At menopause, a woman’s body goes through many changes, including a substantial decrease in the amount of estrogen

produced. Estrogen in your body helps keep bones strong – without it, they may become weak.

Postmenopausal osteoporosis begins without notice; however, over time symptoms develop such as:

- Curved spine
- Rounded shoulders
- Loss of height

Untreated, postmenopausal osteoporosis can be painful and disabling. Some women with postmenopausal osteoporosis suffer from broken hips and fractured wrists. Fortunately, osteoporosis after menopause is treatable. Your doctor or healthcare provider can prescribe a medication, like CALCITONIN-SALMON Nasal Spray, to treat your condition.

How does CALCITONIN-SALMON Nasal Spray work?

The active ingredient in CALCITONIN-SALMON Nasal Spray is calcitonin, a man-made protein similar to one found in people, other mammals, and some types of fish and birds.

The way calcitonin affects bone is still being studied, but it is believed to work in the following ways:

- Calcitonin reduces the activity of osteoclasts [AHS-tee-oh-clasts], the cells that remove "old" bone
- Because bone building continues while bone removal is slowed down, the result is an increase in bone mass

When you spray CALCITONIN-SALMON Nasal Spray into your nostril, it is rapidly absorbed by the blood vessels lining your nasal passages. It then travels into your bloodstream and on to your bones where it works to stop bone loss and helps your bones become stronger.

How do I use CALCITONIN-SALMON Nasal Spray?

The recommended dose of CALCITONIN-SALMON Nasal Spray is one spray daily in alternated nostrils – unless directed otherwise by your healthcare provider. Start with a spray in the left nostril on your first day, followed by a spray in the right nostril on the second day. Continue to alternate nostrils every day. There are at least 30 "doses" of CALCITONIN-SALMON Nasal Spray in each bottle.

You should keep track of the number of doses used from the bottle.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Who should not take CALCITONIN-SALMON Nasal Spray?

CALCITONIN-SALMON Nasal Spray should not be used by patients who are allergic to the protein calcitonin-salmon, or by women who are pregnant or nursing.

You should be aware of these warnings and precautions when taking CALCITONIN-SALMON Nasal Spray.

- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed with the use of CALCITONIN-SALMON Nasal Spray. You should inform your doctor and pharmacist about the other prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking CALCITONIN-SALMON Nasal Spray. For this reason, it is recommended that a nasal examination be performed prior to the start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with CALCITONIN-SALMON Nasal Spray. In some cases, your doctor may decide to temporarily discontinue treatment with CALCITONIN-SALMON Nasal Spray until symptoms subside.
- Because calcitonin-salmon is a protein, the possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use CALCITONIN-SALMON Nasal Spray.
- CALCITONIN-SALMON Nasal Spray is safe to use in elderly patients. A slight increase in nasal

symptoms has been observed in patients over 65 years of age; however, the symptoms are usually mild. No other unusual side effects have been seen in patients over 65 years of age.

Possible Side Effects

Most patients tolerate treatment with CALCITONIN-SALMON Nasal Spray very well; however, like all prescription drugs, CALCITONIN-SALMON Nasal Spray may cause some side effects in some people. These side effects are usually mild and generally do not lead to discontinuation of treatment with CALCITONIN-SALMON Nasal Spray. The most commonly reported side effects are:

- Nasal symptoms such as runny nose, crusting, or nasal bleeding
- Back/joint pain
- Headache

Anytime you have a medical problem you think may be related to CALCITONIN-SALMON Nasal Spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to assemble, prime, and use CALCITONIN-SALMON Nasal Spray. In addition, detailed directions can be found in your CALCITONIN-SALMON Nasal Spray box. Please read them carefully before assembling and using the spray.

This medication is prescribed for a particular condition. Do not use it for another condition or give the drug to others. Keep CALCITONIN-SALMON Nasal Spray and all medicines out of reach of children. This leaflet provides a summary of information about CALCITONIN-SALMON Nasal Spray. If you have any questions or concerns about either CALCITONIN-SALMON Nasal Spray or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other healthcare provider.

HOW TO ASSEMBLE AND USE

CALCITONIN-SALMON NASAL SPRAY, USP

One Spray, Once a Day

BEFORE USING CALCITONIN-SALMON NASAL SPRAY

This package contains one bottle of Calcitonin-Salmon Nasal Spray and one screw on pump.

Important Facts About Your Medication

- The bottle contains the proper amount of medication — be aware that the entire bottle will not be filled with liquid.
- Before opening and assembling your medication bottle, keep it in your refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze.
- After opening and assembling a new medication bottle, keep it at room temperature between 20°C to 25°C (68°F to 77°F) in an upright position.

HOW TO USE CALCITONIN-SALMON NASAL SPRAY

Putting the Nasal Spray Pump Unit Together

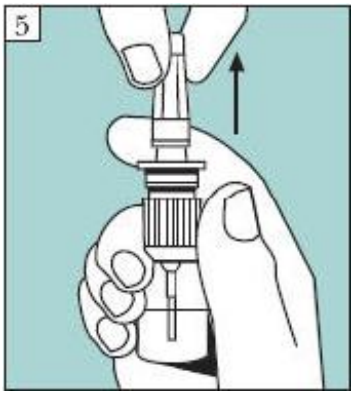
1. If your bottle and pump unit were already assembled by your pharmacist, go to step 6. If not, remove the bottle from your refrigerator and allow it to reach room temperature before assembling.

2. Keeping the bottle upright, unscrew the white cap.

3. Remove the pump from the plastic protection bag.

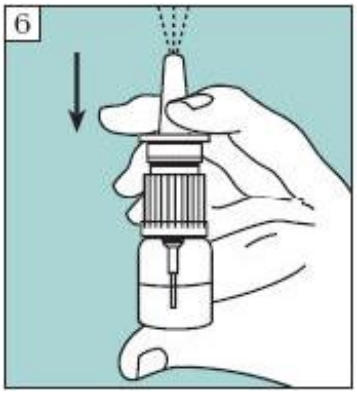
4. Holding the bottle upright, insert the nasal spray pump unit into the bottle. Then turn the pump clockwise, and tighten it until it is securely fastened to the bottle.

Note: Do not depress pump when it is not attached to the bottle.



5. Holding the bottle upright with your index finger on top of one of the two side arms of the pump, gently remove the clear protective cap from the top of the nozzle.

Priming a New Bottle



6. To ensure proper delivery of medication, a newly opened and assembled bottle must be primed before you use it for the first time.

<u>If your pharmacist assembled the unit for you</u>, check to see if it has already been primed by pumping the unit once. If a full spray is emitted, the unit has already been primed. If no spray is emitted, you must prime the unit. Holding the bottle upright with your index and middle fingers on the two side arms of the pump, and your thumb on the bottom of the bottle, press the arms down fully **until you see a full spray**. Now the nasal spray is ready for use.

Do not re-prime the pump before each daily use because this will waste your medication.

Using the Medication

7. The recommended dose of Calcitonin-Salmon Nasal Spray is one spray once a day in one nostril.

Keep your head upright and carefully place the nozzle in one nostril.

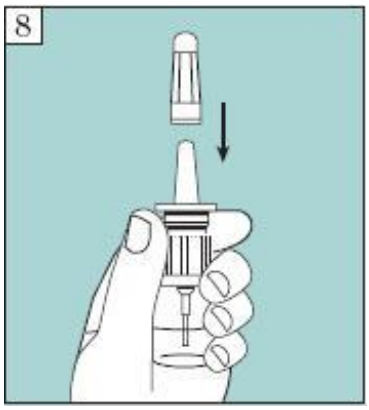
Tilt the bottle until it is in a straight line with the nasal passage.

Firmly press down on the pump once to spray the medication into your nose. It is not necessary to inhale while this is being done. Please note: Because the mist is so fine, you may not feel it inside your nose. Also, some medication may drip out of your nose. However, in either case, the medication is absorbed. IMPORTANT: Do not "test" the spray unit or prime it before you use your daily dose because this will waste your medication.

Cleaning the Pump

Once or twice a week, wipe the nozzle with a clean, damp cloth. Dry the nozzle before replacing the dust cap

Storing the Unit



8. Holding the bottle with two fingers **under** the two side arms of the pump, gently replace the protective cap on the nasal spray unit. **Be careful not to depress the pump** while this is being done. Once the pump is primed, the unit must be kept at room temperature between 20°C to 25°C (68°F to 77°F) in the upright position until the medication is finished.

IMPORTANT

- Do not refrigerate the unit between doses
- Do not store the unit on its side

Bottles left at room temperature (opened or unopened) for more than 35 days must be discarded.

Refrigerated bottles are good until the expiration date stamped on the bottle and box.

Alternate Nostrils Daily

The first day, start with one spray in the left nostril. The next day, use one spray in the right nostril, and so on.

It is important to receive the correct daily amount of calcium and vitamin D, as directed by your healthcare provider.

IMPORTANT

- **Use Calcitonin-Salmon Nasal Spray daily.**

To ensure proper treatment, it is important to use your Calcitonin-Salmon Nasal Spray daily even if you have no symptoms of postmenopausal osteoporosis.

A single spray of Calcitonin-Salmon Nasal Spray, USP contains one daily dose, which is 200 I.U. of calcitonin-salmon. The fine mist is actually 0.09 mL (milliliter) of solution. Your bottle of Calcitonin-Salmon Nasal Spray contains at least 30 doses. Priming the pump as described in step 6 does not alter the total number of doses available in a bottle of Calcitonin-Salmon Nasal Spray. The bottle need only be primed once after assembly. Do not reprime or "test spray" your bottle before you use your daily dose of Calcitonin-Salmon Nasal Spray. This will waste your medication.

Please see your healthcare provider for complete product information for Calcitonin-Salmon Nasal Spray.

Distributed by:

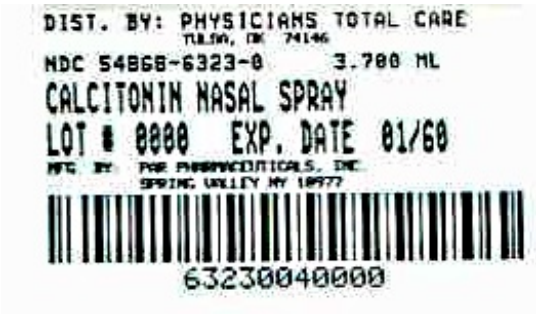
Par Pharmaceutical Companies, Inc.

Spring Valley, NY 10977

Revised: 02/11 OS161-01-1-03

Additional barcode label applied by:
Physicians Total Care, Inc.
Tulsa, Oklahoma 74146

PRINCIPAL DISPLAY PANEL - CARTON



CALCITONIN SALMON

calcitonin salmon spray, metered

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-6323(NDC:49884-161)
Route of Administration	NASAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CALCITONIN SALMON (UNII: 7SFC6U2VI5) (CALCITONIN SALMON - UNII:7SFC6U2VI5)	CALCITONIN SALMON	200 [iU] in 0.09 mL

Inactive Ingredients	
Ingredient Name	**Strength**
HYDROCHLORIC ACID (UNII: QTT17582CB)	
NITROGEN (UNII: N762921K75)	

SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6323-0	1 in 1 CARTON		
1		3.8 mL in 1 BOTTLE, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076979	12/09/2011	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel

Revised: 12/2011 Physicians Total Care, Inc.