PRODUCT MONOGRAPH

[Pr] SANDOZ CALCITONIN NS

Synthetic Calcitonin (Salmon)

Nasal Spray
200 IU/actuation

Bone Metabolism Regulator

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[PR]SANDOZ CALCITONIN NS

Synthetic Calcitonin (Salmon) nasal spray

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Nasal spray	200 IU/actuation	Benzalkonium chloride, hydrochloric acid, sodium chloride and purified water.

INDICATIONS AND CLINICAL USE

Sandoz Calcitonin NS (synthetic calcitonin; salmon) Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in females greater than five years postmenopause with low bone mass relative to healthy premenopausal females. Significant effects on lumbar vertebral bone mineral density , but not on forearm and hip bone mineral density, have been demonstrated. (see Clinical Trials)

Sandoz Calcitonin NS 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.

Geriatrics (> 65 years of age):
Clinical trials using synthetic calcitonin (salmon) nasal spray have included postmenopausal women 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.

Pediatrics (< 18 years of age):
The safety and efficacy of synthetic calcitonin (salmon) nasal spray in children have not been established.

CONTRAINDICATIONS

• Known hypersensitivity to salmon calcitonin (s-calcitonin) or to any component of the formulation (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

WARNINGS AND PRECAUTIONS

Immune

Allergic Reactions
Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. There have been rare reports of serious allergic-type reactions, such as bronchospasm, swelling of the tongue or throat, tachycardia, hypotension, collapse and anaphylactic shock in post marketing. 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.

Skin testing should be considered prior to treatment with synthetic calcitonin (salmon) nasal spray for patients with suspected sensitivities to calcitonin. (see Monitoring and Laboratory Tests section)

Ear/Nose/Throat

Nasal Examinations
Nasal adverse events occurred in 17% of patients who received synthetic calcitonin; (salmon) nasal spray and in 14% of patients who received placebo nasal spray in studies in postmenopausal females. 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 synthetic calcitonin (salmon) nasal spray, the most commonly reported nasal adverse events included rhinitis (8.2%), nasal dryness (3.9%), epistaxis (2.4%), and sinusitis (1.6%). 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, synthetic calcitonin (salmon) nasal spray should be discontinued. Although smaller ulcers often heal without withdrawal of synthetic calcitonin (salmon) nasal spray, medication should be discontinued temporarily until healing occurs.

Special Populations

Pregnant Women: There are no adequate and well controlled studies in pregnant women with s-calcitonin. Synthetic calcitonin (salmon) nasal spray is not indicated in pregnancy.

Synthetic calcitonin (salmon) nasal spray has been shown to cause a decrease in fetal birth weights without any fetal abnormalities in rabbits when given by injection in doses 70-278 times the intranasal dose recommended for human use based on body surface area . Since

synthetic calcitonin (salmon) nasal spray does not cross the placental barrier, this may be due to metabolic effects in the pregnant animal.

Nursing Women: It is not known whether this drug is excreted in human milk and should not be administered to nursing mothers. Synthetic calcitonin (salmon) nasal spray has been shown to inhibit lactation in animals and should not be administered to nursing mothers.

Pediatrics (< 18 years of age): The safety and efficacy of synthetic calcitonin (salmon) nasal spray in children have not been established. Its use is not recommended in pediatrics.

Geriatrics (> 65 years of age): Clinical trials using synthetic calcitonin (salmon) nasal spray have included postmenopausal women 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.

Monitoring and Laboratory Tests

Skin testing should be considered prior to treatment with synthetic calcitonin (salmon) nasal spray for patients with suspected sensitivities to calcitonin. The following procedure is suggested: Prepare a dilution of 10 IU per mL by withdrawing 0.05 mL of commercially available synthetic calcitonin (salmon) solution for injection in a tuberculin syringe and filling it to 1.0 mL with Dextrose Injection 5%, USP (or Saline Injection, USP). Mix well, discard 0.9 mL and inject intracutaneously 0.1 mL (approximately 1 IU) on the inner aspect of the forearm. Observe the injection site 15 minutes after injection. The appearance of more than mild erythema or wheal constitutes a positive response.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly reported adverse events with synthetic calcitonin (salmon) nasal spray were local effects such as rhinitis, nasal dryness with crusting, non-severe epistaxis and sinusitis.

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. When bone resorption is more rapid, decreases in serum calcium are more pronounced in response to calcitonin.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Synthetic calcitonin (salmon) nasal spray has been evaluated for safety in more than 650 patients treated for osteoporosis for up to two years.

Table 1 is based on controlled trials in patients treated with synthetic calcitonin (salmon) nasal spray at doses of 50, 100, 200, or 400 IU/day for up to 2 years. The table includes all AEs with an incidence of 1% or greater in the synthetic calcitonin (salmon) all combined doses treatment group, irrespective of causal relationship to study drug.

In approximately one-half of the patients tested after six months or more of treatment, indications of circulating antibodies to salmon calcitonin were obtained. In most patients the presence of antibodies does not reduce the clinical efficacy of exogenous salmon calcitonin.

Table 1: Common AEs occurring in ≥ 1% of patients receiving synthetic calcitonin (salmon) nasal spray, combined doses treatment group for up to 2 years, by body system (regardless of study drug relationship)

Body system/ Adverse Event	**Synthetic Calcitonin (salmon) nasal spray (n=697) %**	**Placebo (n=389) %**
Respiratory thoracic and mediastinal disorders		
Rhinitis	8.2	5.4
Nasal dryness	3.9	3.6
Epistaxis	2.4	2.1
Nasal Crusting	2.2	2.8
Nasal discomfort	1.6	1.0
Sinusitis	1.6	0.5
Upper Respiratory Tract Infection	1.4	2.3
Nasal Irritation	1.4	1.5
Pharingitis	1.0	1.0
Gastro-intestinal disorders		
Abdominal pain	3.0	1.5
Constipation	1.7	1.8
Nausea	1.7	1.0
Dyspepsia	1.6	0.3
General disorders		
Influenza symptoms	1.6	2.6
Fatigue	1.1	0.3
Vascular disorders		
Hypertension	1.7	0.8
Flushing	4.6	5.1
Nervous system disorders		
Headache	2.7	2.8
Depression	1.6	1.5
Dizziness	1.6	0.8

Musculoskeletal and connective tissue disorders		
Back pain	2.9	0.8
Arthralgia	2.0	1.8
Bone fracture	1.4	1.5
Arthrosis	1.0	1.0
Eye Disorders		
Lacrimation abnormal	1.0	0.8
Infections and infestations		
Cystitis	1.1	1.0
Infection	1.4	1.0

Synthetic calcitonin (salmon) nasal spray has also been evaluated for safety in more than 900 patients, who were at least 1-year postmenopausal, treated for up to 5 years in the Prevent Recurrence of Osteoporotic Fractures (P.R.O.O.F.) Trial. Similar types of adverse reactions were reported in this study. However, the incidence for adverse reactions in this trial, involving 942 patients exposed to synthetic calcitonin (salmon) nasal spray and 307 patients exposed to placebo nasal spray, were generally higher than in the 2 year trials due to the longer observation period. In addition, these events were reported with a similar frequency in both the synthetic calcitonin (salmon) and placebo groups.

Table 2 includes P.R.O.O.F AEs occuring in ≥ 1% of patients receiving synthetic calcitonin (salmon) nasal spray, assessed as definitely, probably, possibly, or unlikely drug related by the investigators.

Table 2: P.R.O.O.F: AEs occurring in ≥ 1% of patients receiving synthetic calcitonin (salmon) nasal spray, regardless of study drug relationship

Body system/ Adverse Event	**Synthetic Calcitonin (salmon) nasal spray (n= 942) %**	**Placebo (n=307) %**
General disorders and administration site conditions		
Edema (e.g. tongue, extremity, face, generalized)	3.1	2.6
Accidental trauma*	1.0	1.3
Asethenia*	1.3	1.0
Chest pain*	2.9	2.9
Hot flushes*	1.3	2.0
Cardiovascular disorders		

Arrhythmia*	1.0	1.6
Gastrointestinal disorders		
Diarrhea	1.8	1.0
Dysgeusia	1.3	1.0
Hearing and Vestibular disorder		
Ear Disorder* (eg sensation of fullness, stuffiness, blockage)	1.0	1.3
Immune system disorders		
Allergy	1.6	1.4
Metabolic and Nutritional disorders		
Hypercalcemia*	1.7	1.3
Muscoluskeletal disorders		
Arthropathy*	5.5	5.9
Leg pain*	2.2	2.3
Pain* (eg musculoskeletal, general)	4.5	5.5
Nervous system disorders		
Headache	3.9	7.2
Dysphonia*		
Somnolence*		
Respiratory, thoracic and mediastinal disorders		
Rhinitis (including nasal edema, nasal congestion, sneezing, allergic rhinitis)	30.6	20.8
Nasal discomfort (e.g. nasal odour, nasal mucosal erythema, mucosal excoriation).	15.8	13.0
Epistaxis	12.6	11.7
Rhinitis ulcerative	3.4	1.6
Abnormal Chest Sounds* (eg basilar, crepitations, rales)	1.2	1.0
Skin Disorders		
Skin disorder* (eg fissures,leisions, sores)	1.6	0.7
Dry skin*	1.1	0.3
Vascular Disorder		
Purpura	1.3	0.7
Vision disorders		
Cataract*	2.8	1.3
Eye abnormality* (dryness, infection, irritation)	1.2	2

Glaucoma*	1.0	0.0

*additional adverse reactions that occurred in the P.R.O.O.F. trial not included in the 2 years trial data.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Gastrointestinal disorders: Nausea, vomiting. These effects usually subsided spontaneously.

General disorders and administration site conditions: Dizziness, flushing accompanied by a sensation of heat and chills. These effects usually subsided spontaneously.

Genito-urinary disorders: Uncommonly polyuria. These effects usually subsided spontaneously.

Immune system disorders: synthetic calcitonin (salmon) nasal spray may give rise to hypersensitivity reactions such as generalized skin reactions, flushing, edema (facial, extremity and generalized), hypertension and arthralgia. Allergic and anaphylactoid-like reactions and single case of anaphylactic shock have been reported.

Respiratory, thoracic and mediastinal disorders: Nasal polyp, nasal septum ulceration, and nasoseptal deviation. Most of the nasal events were mild to moderate in severity and did not prompt discontinuation. Synthetic calcitonin (salmon) nasal spray nasal adverse event rates were 73.5% mild, 24.3% moderate, and 2.2% severe (placebo nasal spray adverse event rates were 69.5% mild, 24.3% moderate, and 6.2% severe).

Abnormal Hematologic and Clinical Chemistry Findings

Antibodies to salmon calcitonin	In approximately one-half of the patients tested after six months or more of treatment, indications of circulating antibodies to salmon calcitonin were obtained. In most patients the presence of antibodies does not reduce the clinical efficacy of exogenous salmon calcitonin.
Urine sediment abnormalities	Urine sediment abnormalities have not been reported in ambulatory volunteers treated with synthetic calcitonin (salmon) nasal spray. Coarse granular casts containing renal tubular epithelial cells were reported in the urine of young adult volunteers at bed rest who were given injectable synthetic calcitonin (salmon) in order to determine the effect of synthetic calcitonin (salmon) on immobilization osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after salmon calcitonin therapy was stopped.

Post-Market Adverse Drug Reactions

Rash generalised, pruritis, cough, isolated anaphylactic-type reactions and anaphylactoid reactions including tachycardia, hypotension and collapse. Single case of anaphylactic shock have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Formal studies designed to evaluate drug interactions with s-calcitonin have not been conducted.

Drug-Food Interactions

The interaction of synthetic calcitonin (salmon) nasal spray with food has not been studied.

Drug-Herb Interactions

The interaction of synthetic calcitonin (salmon) nasal spray with herbal medications or supplements has not been studied.

Drug-Laboratory Interactions

The interaction of synthetic calcitonin (salmon) nasal spray with laboratory tests has not been studied.

Drug-Lifestyle Interactions

Effect on ability to drive and use machines: No studies exist on the effects of synthetic calcitonin (salmon) nasal spray on ability to drive and use machines. synthetic calcitonin (salmon) nasal spray may cause fatigue, and visual disturbances, which may impair the patient's reactions. Patients must therefore be warned that these effects may occur, in which case they should not drive or use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Pediatrics (< 18 years of age): The safety and efficacy of synthetic calcitonin (salmon) nasal spray in children have not been established. Use is therefore not recommended.

Elderly (> 65 years of age): Clinical trials using synthetic calcitonin (salmon) nasal spray have included postmenopausal women up to 77 years of age.

Recommended Dose and Dosage Adjustment

The recommended dose of Sandoz Calcitonin NS (synthetic calcitonin; salmon) nasal spray in postmenopausal women is one spray (200 IU i.e 0.2 mcg) 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 mass or increases in bone density.

Missed Dose

Patients who miss one dose of Sandoz Calcitonin NS (salmon calcitonin) should not increase the dose of Sandoz Calcitonin NS to compensate for the missed dose or doses, but should continue with therapy as soon as possible.

Administration

Instructions on priming of the pump upon first use of the device and nasal introduction of Sandoz Calcitonin NS (synthetic calcitonin; salmon) Nasal Spray should be given to the patient. Instructions for patients are supplied with individual bottles. Patients should be asked to notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Upon, first use only, the pump must be primed. The product should be allowed to reach room temperature before priming.
- After priming and first use, the product should be stored at room temperature in an upright position. Each bottle contains 14 doses.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Nausea, vomiting, flushing and dizziness are known to be dose dependent when synthetic calcitonin (salmon) is administered parenterally. Such events might therefore also be expected to occur in association with an overdose of synthetic calcitonin (salmon). Treatment would be symptomatic. Isolated cases of overdose have been reported but no serious adverse reactions have been associated with high doses.

Single doses of synthetic calcitonin (salmon) nasal spray up to 1600 I.U. and doses up to 800 I.U. per day for three 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 synthetic calcitonin (salmon) injectable solution given subcutaneously may produce nausea and vomiting. A dose of synthetic calcitonin (salmon) injectable solution of 32 I.U. per kg per day for one or two days demonstrated no additional adverse effects.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Salmon calcitonin (s-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. It is of physiological importance in the regulation of calcium metabolism in certain animal species and may also have physiological importance in certain extraskeletal systems (e.g., GI and renal function).

Synthetic calcitonin (salmon) nasal spray markedly reduces the removal of calcium from bone in conditions with an increased rate of bone resorption such as osteoporosis. Osteoclast activity is inhibited, and osteoblast formation and activity seem to be stimulated. Synthetic calcitonin (salmon) inhibits bone resorption, thus lowering abnormally increased serum calcium. Additionally, at the beginning of treatment it increases the urinary excretion of calcium, phosphorus, and sodium by reducing their tubular re-uptake. Serum calcium, however, is not reduced below the normal range.

Salmon calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Salmon calcitonin 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 actions of calcitonin on bone and its role in normal human bone physiology are still incompletely understood.

Single injections of synthetic calcitonin (salmon) result in 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 reduction in their resorptive activity. Decreased osteocytic resorption may also be involved.

Because of its chemical nature (a peptide of 32 amino acids), calcitonin may be administered parenterally to achieve maximal absorption. Small percentages of the dose are apparently absorbed when administered by the buccal, oral, topical or inhalation routes; thus far, only the nasal absorption has been well substantiated and demonstrated to show a significant clinical effect.

Pharmacodynamics

All calcitonin structures consist of 32 amino acids in a single chain, with a ring of seven amino-acid residues at the N-terminus, the sequence of which differs from species to species. Synthetic 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. Due to the greater affinity of salmon calcitonin to receptor binding sites than calcitonins from mammalian species, including the synthetic human calcitonin, synthetic calcitonin (salmon) nasal spray is more potent and

longer acting. In terms of bioactivity, the potency of synthetic calcitonin (salmon) nasal spray was found to be about half that of the drug given by i.m. or s.c. injection.

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue architecture leading to enhanced bone fragility and consequent increase in fracture risk. 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.

The primary action of calcitonin is on bone. Studies have shown that calcitonin most consistently affects the osteoclasts. These cells show decreased function, altered morphology and decreased numbers under the influence of calcitonin. Osteocytic osteolysis also appears to be depressed by this hormone. These effects result in the inhibition by calcitonin of bone resorption. Calcitonin may also stimulate osteoblastic bone formation, but decreases in osteoblastic function have also been reported and final conclusions are not yet possible.

Pharmacokinetics

Absorption: The data on bioavailability of synthetic calcitonin (salmon) obtained by various investigators using different methods show great variability, with a range varying between approximately 3 and 50% relative to intramuscular administration. As is the case with other polypeptide hormones, plasma levels of s- calcitonin are not predictive of the therapeutic response, and hence s-calcitonin activity should be evaluated by biochemical or clinical parameters. Synthetic calcitonin (salmon) nasal spray is absorbed rapidly by the nasal mucosa. Maximum plasma concentrations occur within the first hour of administration (median about 10 minutes).

The absolute bioavailability of synthetic calcitonin (salmon) is about 70% after either intramuscular or subcutaneous injection.

Distribution: In the dose range 100–400 IU, area under the plasma concentration curve (AUC) increases roughly in proportion to the dose. However, administration of doses higher than 400 IU does not result in further increases in the AUC for the drug.

The apparent volume of distribution is 0.15 - 0.3 L/kg, and protein binding amounts to 30-40%.

Metabolism: The patterns of tissue distribution of the hormone seem to differ for the three source species studied thus far and correlate with sites of degradation. Thus, porcine calcitonin tends to accumulate in the liver and kidney and both tissues degrade this form. Human calcitonin shows similar properties except that the kidney is relatively more important for the metabolism of human calcitonin than for porcine calcitonin. In the case of salmon calcitonin, accumulation and degradation seem to occur almost exclusively in the kidney.

Excretion: In the case of salmon calcitonin, accumulation and degradation seem to occur almost exclusively in the kidney. Degradation of all forms of calcitonin occurs by splitting the molecule into smaller fragments which are biologically and immunologically inactive. Very

little renal excretion of the intact calcitonin molecule takes place. It appears that salmon calcitonin cannot cross the placental barrier.

For synthetic calcitonin (salmon) nasal spray, the half-life of elimination of synthetic calcitonin (salmon) is calculated to be around 20 minutes. There is no accumulation of the drug on repeated admnistration at 10-hour intervals for up to 15 days.

After either intramuscular or subcutaneous injection the elimination half-life is 70 to 90 minutes . Synthetic calcitonin (salmon) and its metabolites are excreted up to 95% by the kidney, the fraction of the parent drug being 2%.

Special Populations and Conditions

Pediatrics: The safety and efficacy of synthetic calcitonin (salmon) nasal spray in children have not been established.

Geriatrics: Clinical trials using synthetic calcitonin (salmon) nasal spray have included postmenopausal women 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.

STORAGE AND STABILITY

Unopened Sandoz Calcitonin NS Nasal Spray should be stored in the refrigerator between 2 and 8°C and protected from freezing.

After priming, Sandoz Calcitonin NS Nasal Spray should be stored at room temperature (between 15-30°C) and used within 4 weeks. To ensure correct delivery, the bottle should be kept in an upright position.

SPECIAL HANDLING INSTRUCTIONS

To ensure correct delivery, the bottle should be kept in an upright position.

Upon, first use only, the pump must be primed. The product should be allowed to reach room temperature before priming.

Pull up the protective cap, holding the bottle in an upright position, press down the upper part until it clicks. Repeat twice. After the first time the dose counter window shows white and red lines, after the second time white, and after the third time green. It is now ready for use.

After priming and first use, the product should be stored at room temperature in an upright position. Each bottle contains at least 14 doses.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Calcitonin NS (synthetic calcitonin; salmon) Nasal Spray is available in spray bottles delivering at least 14 metered doses of 200 International Units (IU), one unit corresponding to about 0.2 mcg of synthetic calcitonin (salmon). Sandoz Calcitonin NS spray bottles also contains the following nonmedicial ingredient: benzalkonium chloride, hydrochloric acid, sodium chloride and purified water.

Each pack contains 2 bottles of spray solution. The device is composed of a clear, uncoloured glass bottle (glass type I) and a spray mechanism containing an integrated, automatic dose-counting mechanism and a built-in mechanical stop.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: salcatonin ; calcitonin salmon

Chemical name: L-Hemicystinyl-L-seryl-L-asparaginyl-L-leucyl-L-seryl-L-threonyl-L-hemicystinyl-L-valyl-L-leucyl-glycyl-L-lysyl-L-leucyl-L-seryl-L-glutaminyl-L-glutamyl-L-leucyl-L-histidyl-L-lysyl-L-leucyl-L-glutaminyl-L-threonyl-L-tyrosyl-L-propyl-L-arginyl-L-threonyl-L-asparaginyl-L-threonyl-glycyl-L-seryl-glycyl-L-threonyl-L-prolinamic-polyacetate-polyhydrate.

Molecular formula and molecular mass: $C_{145}H_{240}N_{44}O_{48}S_2$ + X CH_3COOH + Y H_2O
3,431.88 + X 60.1 + Y 18.0

Structural formula:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-
1 2 3 4 5 6 7
Val-Leu-Gly-Lys-Leu-Ser-Gln-
8 9 10 11 12 13 14
Glu- Leu- His- Lys -Leu- Gln -
15 16 17 18 19 20
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
21 22 23 24 25 26 27
Gly-Ser-Gly-Thr- Pro-NH2 .X CH3COOH . YH_2O
28 29 30 31 32

Physicochemical properties: A white or almost white, light powder. Freely soluble in water

CLINICAL TRIALS

Treatment of osteoporosis in postmenopausal women

Effect on bone mineral density (BMD)

Study demographics and trial design

Two randomized placebo controlled trials were conducted in 325 postmenopausal females.

Table 3: Summary of patient demographics for clinical trials in postmenopausal women (effect on bone mineral density)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=325)	Mean age (Range)	Gender
SMC 522	Randomised, double blind, placebo-controlled,	Synthetic Calcitonin (salmon) Nasal Spray 50 IU O.D. 100 IU O.D. 200 IU O.D. + 500 mg /day of oral calcium 2 years	"Established"† postmenopausal women 52 patients 52 patients 52 patients	68-72	Female
		Placebo Nasal Spray O.D. + 500 mg daily oral calcium 2 years	52 patients		
SMC 514	Randomised, double blind, placebo-controlled,	synthetic calcitonin (salmon) nasal spray 200 IU O.D.	36 patients	48-64	female
		synthetic calcitonin (salmon) nasal spray 200 IU 3 times / week (MWF)	35 patients		
		Placebo NS O.D. or 3 times / week (MWF)	46 patients		

† Women who were greater than 5 years postmenopause

The two randomized placebo controlled trials were conducted in 325 postmenopausal females with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females.

In other studies calcitonin has been shown to reduce bone resorption stimulated by Vitamin D, Vitamin A or parathyroid hormone. The possible usefulness in promoting fracture healing in animal studies has been reported; further work is needed before conclusions can be reached.

Study results

Table 4: Study results in postmenopausal women (effect on bone mineral density)

Study #	**Lumbar Vertebral BMD Mean Percent Change from Baseline in Valid Completer Patients between Synthetic Calcitonin (salmon) nasal spray vs Placebo**					
SMC 522	**Treatment Group**	**Baseline Mean ± SD[1]**	**Month 6 % Δ [2] (p-value)**	**Endpoint/ Month 12 % Δ (p-value)**	**Month 18 % Δ (p-value)**	**Endpoint/ Month 24 % Δ (p-value)**
	50 IU O.D.	0.778 ± 0.142	1.08 (0.294)	2.25 (0.029)	1.55 (0.046)	1.55 (0.042)
	100 IU O.D.	0.795 ± 0.124	1.30 (0.169)	1.33 (0.254)	1.90 (0.013)	1.45 (0.053)
	200 IU O.D.	0.806 ± 0.135	1.78 (0.042)	2.44 (0.015)	1.76 (0.022)	2.05 (0.007)
	Placebo	0.788 ± 0.142	0.34	0.45	0.13	0.004
SMC 514		**Established Postmenopausal Patient % Δ [2] (p-value)**	**Early Postmenopausal Patient % Δ [2] (p-value)**			
	200 IU O.D.	1.38 (0.007)	-2.06 (0.322)			
	200 IU MWF	-1.14 (0.582)	-3.16 (0.952)			
	Placebo	-1.73	-3.10			

[1]: Standard Deviation
[2]: Mean Percent Change from Baseline

These studies conducted over two years demonstrated that 200 I.U. daily of synthetic calcitonin (salmon) nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in females with osteoporosis or osteopenia who were greater than 5 year postmenopause. Synthetic calcitonin (salmon) nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as six months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of synthetic 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 one year of treatment changing to a trend at 2 years that was no longer statistically significant.

Effect on fracture incidence

Study demographics and trial design

The Prevent Recurrence of Osteoporotic Fractures Trial P.R.O.O.F. study included results from 1255 patients who were at least 1 year postmenopausal with a lumbar spine BMD of at least 2 standard deviations below the mean for young adult females, and at least 1 but not more than 5 thoracic or lumbar vertebral compression fractures at study entry. All patients received a daily supplement of 1000 mg calcium and 400 I.U. vitamin D.

Table 5: Summary of patient demographics for clinical trials in postmenopausal women (effect on fracture incidence)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=325)	Mean age (Range)	Gender
320 P.R.O.O.F[†]	Multicenter, multinational, double blind	Synthetic Calcitonin (salmon) Nasal Spray 100 IU O.D. 200 IU O.D. 400 IU O.D. + oral calcium 1000 mg O.D + vitamin D 400 I.U O.D. 5 years	 316 patients 316 patients 312 patients	Patients who were at least one year postmenopausal	Female
		Placebo NS + oral calcium 1000 mg O.D + vitamin D 400 I.U O.D. 5 years	311 patients		

[†]: The Prevent Recurrence of Osteoporotic Fractures trial

Study results

Table 6: Study results in postmenopausal women (effect on fracture incidence)

Study #	The risk of new vertebral fractures for Synthetic Calcitonin (salmon) nasal spray vs Placebo (p-value)	The risk of new and/or worsening vertebral fractures for Synthetic Calcitonin (salmon) nasal spray vs Placebo (p-value)
P.R.O.O.F	36% lower for synthetic calcitonin (salmon) 200 IU vs placebo (p=0.020)	28 % lower for synthetic calcitonin (salmon) vs placebo (p=0.064)

Based on a protocol scheduled 3-year all accrued data analysis, there was a statistically significant and clinically meaningful reduction in the proportion of patients experiencing new vertebral fractures with synthetic calcitonin (salmon) nasal spray 200 I.U. daily as compared to placebo.

In addition, synthetic calcitonin (salmon) nasal spray 200 I.U. /day reduced the proportion of patients experiencing multiple incident new and/or worsening vertebral fractures by 35% (25/286 in the 200 I.U. group versus 36/269 in the placebo group).

A 2 year supportive study (Study 522; Overgaard) included results from 208 patients, who received a daily supplement of 500 mg calcium, and were greater than 5 years postmenopause without previous fracture. The results of the incidence of new vertebral fractures was approximately two-thirds less in those patients who received synthetic calcitonin (salmon) nasal spray (doses ranging from 50 I.U. to 200 I.U. daily) compared with those who received placebo.

Circulating antibodies to salmon calcitonin after up to 60 months of treatment with synthetic calcitonin (salmon) nasal spray 200 IU were reported in about half of the patients with osteoporosis in whom antibody studies were done. However the presence of circulating antibodies to synthetic calcitonin (salmon) does not reduce the clinical efficacy of the drug and, in addition, it has been suggested that antibody binding may actually prolong the activity of salmon calcitonin, perhaps through a slowing of the catabolism of this polypeptide.

DETAILED PHARMACOLOGY

Animal Studies

Calcitonin, particularly the salmon form, is extremely potent. As little as one nanogram given subcutaneously to young rats lowers the serum calcium by 1-2 mg%. Standardization of potency is based upon rat bioassay versus standards prepared by the Medical Research Council. Recently an official standard has been prepared (International Reference Preparation of Calcitonin, Salmon, for Bioassay). One International Unit (IU) = 1 MRC Unit.

Following parenteral administration, calcitonin is rapidly absorbed into the blood. Its half-life in the circulation, like that of other peptide hormones, is measured in minutes rather than hours. Salmon calcitonin, however, exhibits a relatively longer half-life than does porcine or human calcitonin. Immediately after introduction into the circulation, calcitonin is present in the free form. Later it is largely protein bound, but this does not appear to interfere with either its biological or immunological activity.

By virtue of its ability to inhibit bone resorption, calcitonin decreases the flow of calcium from bone to blood and thus tends to lower blood calcium. The hypocalcemic effect of calcitonin is most marked when bone turnover proceeds at a high rate. Thus, decreases in serum calcium in young animals are more pronounced than those in adults.

The lowering of serum calcium with calcitonin can, under certain conditions, be as much as 3 to 4 mg% and this led to speculation that the hormone might induce hypocalcemic tetany. One case of symptoms of hypocalcemic tetany accompanying administration of human calcitonin has been reported. This symptom disappeared on administration of calcium salts.

Since no reliable model of the pathophysiology of diseases of bone metabolism in man exists, investigations are thereby limited. Salmon calcitonin is effective in preventing or reducing experimentally induced bone loss in a number of animal models (i.e. calcitonin inhibition of bone resorption and associated increase in bone mass/density).

In other studies calcitonin has been shown to reduce bone resorption stimulated by Vitamin D, Vitamin A or parathyroid hormone. The possible usefulness in promoting fracture healing in animal studies has been reported; further work is needed before conclusions can be reached.

Actions of calcitonin on gastrointestinal function have clearly been shown, though these are not yet fully understood. Variable effects on calcium absorption by the GI tract have been reported, with an increase in absorption the effect most frequently noted. In this regard, calcitonin could be acting directly or the hormone could invoke increased formation of 1, 25-dihydroxycholecalciferol which in turn would increase the absorption of calcium. Finally, the effect could be mediated by a secondary parathyroid mechanism whereby PTH, either directly or via the vitamin D mechanism, would act to enhance calcium absorption.

Other actions of calcitonin on GI function include an ability to decrease the volume and acidity of gastric secretions, as well as an inhibition of exocrine volume and enzyme secretion by the pancreas. Attempts to inhibit ulcer formation in animal experiments by reducing gastric secretion with calcitonin were successful in two studies.

Renal effects of calcitonin are well documented. It appears that calcitonin decreases the tubular reabsorption of calcium, leading to increased excretion of this ion (when other factors are not involved). Analogous effects of calcitonin are seen in magnesium handling, though the mechanism of this effect is somewhat less clear than for calcium. Sodium and phosphorus also experience decreased tubular reabsorption due to calcitonin. For these ions the effects appear to involve the proximal tubules. Actions of calcitonin on the handling of calcium and sodium by the kidney seem to be separate. In animal studies, salmon calcitonin appears to be markedly more natriuretic than porcine or human calcitonin though the effects of the hormone from these different species on calcium excretion are relatively similar. Potassium excretion is sometimes

increased and sometimes unchanged by calcitonin. Increased excretion of water also occurs. Calcitonin appears to have little effect on glomerular filtration rate.

There are two modifying factors which are important in any consideration of the renal effects of calcitonin. The first involves a decrease in filtered load of calcium due to the hypocalcemic effect of the hormone. In acute situations especially, the decrease in tubular reabsorption of this ion results in a decrease rather than an increase in urinary calcium excretion. The second factor is increased parathyroïd hormone (PTH) secretion, secondary to the hypocalcemic effect of calcitonin. PTH acts directly on the kidney to increase the tubular reabsorption of calcium and magnesium and to decrease the reabsorption of phosphorus. The first two actions of PTH oppose those of calcitonin, while the effect on phosphorus complements the action of calcitonin. In any given situation the overall effects of calcitonin on urinary excretion are dependent upon several factors and the results can vary accordingly.

The dose level of calcitonin may also influence renal excretion, at least in regards to calcium. The effect of calcitonin on bone resorption appears to be more sensitive than is the effect on the renal tubular reabsorption of calcium. Thus, at low doses, calcitonin can sometimes lower urinary calcium excretion because of its effect on filtered load. At high doses the direct renal effect tends to predominate which results in an increased excretion of urinary calcium.

PTH secretion is directly controlled by levels of serum calcium, and acute decreases in the latter, caused by calcitonin, result in immediate increases in circulating levels of PTH. Chronic treatment with calcitonin could, therefore, conceivably give rise to hyperplasia of the parathyroids and increased levels of basal PTH secretion (secondary hyperparathyroidism). Certain animal data appear to support this possibility. There is also a reason to believe that the enhanced secretion of PTH during calcitonin administration modifies the effects that would otherwise be produced. For some effects PTH may tend to antagonize and minimize the actions of calcitonin. In other instances in the same animal, the effects of PTH and calcitonin may complement and reinforce one another.

For example, as explained above, calcitonin and PTH have opposite effects on the tubular reabsorption of calcium but reinforce each other in their actions on phosphate excretion. On bone the interactions of PTH and calcitonin are perhaps more important but less well understood. Increased PTH levels lead to enhanced osteoclastic activity, while calcitonin has the opposite effect. The outcome when both are present in continuing high levels has not been clarified. Interactions of these hormones on other bone cells are even less well understood. Increased levels of PTH have been implicated in enhanced bone formation, as well as increased bone resorption; both may prove to be significant factors in the long-term skeletal effects with chronic calcitonin treatment. Based on indirect evidence, cessation of calcitonin treatment appears to be associated with a return toward the pretreatment level of PTH secretion.

Repeated treatment of animals with very high doses of calcitonin has led to several unexplained changes. In a one month study in rabbits, histological changes were reported in follicular cells of the thyroid indicative of a hypersecretory state; changes were also noted in the parafollicular cells. In studies in young rats, treatment for seven days consistently led to decreases in thyroid and heart weight and to increases in red cell counts.

Human Studies

Kidney

Salmon calcitonin increases the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. In some patients the inhibition of bone resorption by salmon calcitonin is of such magnitude that the consequent reduction of filtered calcium load more than compensates for the decrease in tubular reabsorption of calcium. The result in these patients is a decrease rather than an increase in urinary calcium.

Transient increases in sodium and water excretion may occur after the initial injection of salmon calcitonin. In most patients these changes return to pretreatment levels with continued therapy.

Gastrointestinal tract

Some evidence 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 secretions and in the volume and the trypsin and amylase content of pancreatic secretions. Whether these effects continue to be elicited after each injection of salmon calcitonin during chronic therapy has not been investigated. These studies have not been conducted with synthetic calcitonin (salmon) nasal spray.

TOXICOLOGY

Synthetic salmon calcitonin has been administered to animals acutely, subchronically and chronically by intravenous, subcutaneous and intramuscular routes. Rats, rabbits and dogs were used for these studies. Teratogenicity as well as perinatal and postnatal studies were conducted in rats and rabbits. The studies were carried out according to standard protocols. A sensitization study in guinea pigs was also completed because of the chemical nature of calcitonin.

Chronic Toxicity

Dogs given salmon calcitonin subcutaneously for six months at dosage levels of 20 to 80 units/kg/day exhibited partial to total anorexia with concurrent body weight loss during the first few weeks of the study. Thereafter, food consumption was similar in control and treated dogs.

Synthetic salmon calcitonin was administered subcutaneously at levels of 20 to 80 units/kg/day from day 15 of gestation through lactation in a perinatal and postnatal study. In this study there appeared to be a partial to complete failure in lactation in some treated dams. One litter in each of the treated groups gradually became cachectic before day 9 of lactation and died. Macroscopically the kidneys of several rats in both treated groups appeared mottled. Microscopically, hyaline casts in the medulla and cortex, dilatation of cortical tubules, interstitial nephritis (not associated with cast formation), and fat droplets and brown pigment in cortical tubular cells were seen. The following parameters in pups of treated dams were affected: pup weight at 24 hours, 4 days and 21 days, and lactation index.

In a repeat of the perinatal and postnatal study in rats, body weight of pups in treated groups was less than control pups, and the rate of stillbirth was more for pups of treated dams than for control pups. No macroscopic kidney changes were noted in dams. Microscopically the kidneys of several of the dams treated with 20 or 80 units/kg/day exhibited dilatation of renal collecting tubules with homogeneous casts. No such kidney changes were noted in dams treated with 5 units/kg/day.

In a third perinatal and postnatal study in rats, treatment with 320 units/kg/day from day 15 of pregnancy through the lactation period caused renal tubule dilatation and associated hyaline cast formation in 3 of 10 dams. No significant effect was noted in pups.

The sensitization study indicated that salmon calcitonin had no sensitizing potential in guinea pigs.

Nasal Tolerability

Long-term studies

The tolerance of synthetic calcitonin (salmon) nasal spray was assessed in the cynomolgus monkey following intranasal administration of 0 (control), 400, 800, and 1600 I.U./day for 26 weeks. No treatment related effects were noted with respect to clinical signs, body weight, ophthalmoscopy, and clinical chemistry. Macroscopic and microscopic examination of the respiratory tract and other tissues did not reveal any treatment related changes. There was no effect on bone mass, histomorphometric analysis of the bone did not reveal any differences in the indices investigated between treated and vehicle control group animals.

Probable treatment related effects on urinary parameters and kidney weights were apparent, although the changes observed were generally small and did not show a clear dosage relationship. The changes may be anticipated as it has been reported that calcitonin can exert an effect on the kidney, although the precise mechanism is not known. It was concluded that synthetic calcitonin (salmon) nasal spray was tolerated in the monkey at dosages up to 1600 I.U./day. The effects on urinary parameters and kidney weight were considered to represent a functional effect rather than an adverse effect to the treatment since no macroscopic or microscopic changes were observed in the kidney.

Short-term studies

Synthetic salmon calcitonin spray (200 I.U.) was administered intranasally six times a day for 4 weeks to 4 male and 4 female beagle dogs. No signs of reaction to treatment were detected including the nasal cavity and upper respiratory tract, and none of the animals died. Food consumption and body weight were normal. Physical examination after 3 weeks was unremarkable. Necroscopy did not reveal any treatment-related lesions or differences in organ weights.

A similar study in guinea pigs assessed the ciliary beat frequency (CBF) after 4 week intranasal administration of synthetic salmon calcitonin solution. Thirty guinea pigs received 2 x 0.01 mL (400 I.U.) salmon calcitonin solution daily for 4 weeks. Measurements on CBF were taken immediately, 24 hours, and at 15 days after dosing in different treatment groups. It was concluded that the treatment showed no adverse effects on ciliary activity.

Local tolerability

Synthetic salmon calcitonin (200 I.U./0.01 mL) was administered by single instillation into the ocular sac of 3 male and 3 female albino New Zealand white rabbits. The study animals were examined one and 24 hours, and 2, 3, 4 and 7 days post-treatment. No overt effect upon the cornea, iris or conjunctivae of any rabbit was detected.

Carcinogenicity

Long-term Studies

Synthetic salmon calcitonin was administered subcutaneously (1.25-80 IU/kg/day) to 153 male and female sprague Dawley rats. An increase in the incidence of pituitary tumors was seen predominantly in the male and to a lesser degree in the female rats. Pituitary histopathology revealed a significant ($p < 0.01$) increase in the chromophobe cell adenomas in males receiving 20 IU/kg/day or more.

In two other studies, synthetic salmon calcitonin was not shown to induce the hyperplastic/neoplastic process, as a similar incidence of total proliferative lesions was observed in control and treated (80 IU/kg/day) animals. The latency period for the development of pituitary adenomas was however, reduced. This type of endocrine lesion is particularly common in the rat, a change in latency may be attributed to the disruption of the normal physiologic process involved in the development of the endocrine lesion in the rat.

Continuous administration of 80 IU/kg/day of synthetic salmon calcitonin with osmotic pumps seemed to reduce the latency period for the development of hyperplastic foci as compared to the subcutaneous injection of the same dose of calcitonin.

Short-term Studies

Synthetic salmon calcitonin was administered subcutaneously (20 IU/kg/day) in rats, either alone or in combination with diethylstilbestrol and/or bromocriptine for 8 weeks. The results obtained suggest that salmon calcitonin does not act directly or indirectly on lactotrophs to stimulate a proliferative response in the pituitary. A 3-month subcutaneous study of calcitonin (5 or 160 IU/kg/day) and disodium EDTA (150 mg/kg/day) revealed that it is not the calcium lowering activity of the drug which is responsible for the increase in incidence of pituitary lesions in rats. Subsequently, a combination of serum assays, immunohistochemical and Northern blot analyses have shown that the majority of proliferative lesions in the rats are non-functional and comprise cells which produce an alpha subunit common to glycoprotein hormones (LH, TSH, FSH). Moreover, the histomorphology of the proliferating non-functional lesions was consistent with lesions that occur spontaneously in aged laboratory rats.

Evidence suggests that the proliferative response in the pituitary of rats is a species-specific phenomenon. Similar findings have not been observed in mice treated with subcutaneous synthetic salmon calcitonin in doses ranging from (0.625 to 160 IU/kg/day) for periods of 13 weeks to 18 months, nor in dogs treated subcutaneously with synthetic salmon calcitonin (5 to 80 IU/kg/day) for 16 weeks.

Teratology

In a teratogenicity study in rats wherein synthetic salmon calcitonin was administered from day 6 through day 20 of gestation at 20 to 80 units/kg/day subcutaneously, two of 20 dams receiving the higher dosage level exhibited coarse tan mottling of both kidneys. In a repeat study in the same strain of rats no such macroscopic kidney changes were noted, and there were no microscopic pathologic changes in the kidneys related to treatment with salmon calcitonin.

In a teratogenicity study in rabbits, the mean fetal weight was decreased at 80 and 20 units/kg/day and the mean placental weight was decreased at 80 units/kg/day.

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PART III: CONSUMER INFORMATION

[PR]Sandoz Calcitonin NS
Synthetic Calcitonin (Salmon) Nasal Spray

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Calcitonin NS Nasal Spray was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandoz Calcitonin NS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Calcitonin NS is used in the treatment of postmenopausal osteoporosis in women, in addition to exercises and adequate calcium and vitamin D intake.

What it does:
Sandoz Calcitonin NS reduces the removal of calcium from bone in conditions with an increased rate of bone resorption such as osteoporosis.

What is Osteoporosis?
Osteoporosis is a thinning and weakening of the bones that is common in postmenopausal women. The menopause occurs when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). After the menopause, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. The earlier a woman reached the menopause, the greater the risk of osteoporosis. Maintaining bone mass and preventing further bone loss are important to keep your skeleton healthy.

Early on, osteoporosis usually has no symptoms, if left untreated, however, it can result in fractures (broken bones). Although fractures usually cause pain, fractures of the bones of the spine may go unnoticed until they cause height loss. Fractures may occur during normal, everyday activity, such as lifting, or from minor injury that would not ordinarily fracture normal bone. Fractures usually occur at the hip, spine, or wrist and can lead not only to pain, but also to considerable deformity and disability (such as stooped posture from curvature of the spine, and loss of mobility).

When it should not be used:
You should not take Sandoz Calcitonin NS if you are allergic to salmon calcitonin or to any nonmedicinal ingredients of Sandoz Calcitonin NS.

If you think you may be allergic to Sandoz Calcitonin NS solution, ask your doctor for advice. You may need to undergo a skin test before you start your treatment.

What the medicinal ingredient is:
Synthetic calcitonin (salmon)

What the important nonmedicinal ingredients are:
Benzalkonium chloride (as a preservative), hydrochloric acid (for pH adjustment), sodium chloride and purified water.

What dosage forms it comes in:
Sandoz Calcitonin NS is available in spray bottles delivering at least 14 metered doses. Each metered dose delivers 200 IU synthetic calcitonin (salmon)

WARNINGS AND PRECAUTIONS

BEFORE you use Sandoz Calcitonin NS talk to your doctor or pharmacist if:
• You have chronic rhinitis
• You are pregnant or planning to get pregnant
• You are breast feeding
Sandoz Calcitonin NS can cause serious allergic reactions. Sandoz Calcitonin NS should not be used in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicine including those not prescribed by a doctor.

It is particularly important that you tell your doctor if you are taking a medicine containing lithium.

PROPER USE OF THIS MEDICATION

Usual dose: one spray (200 IU) once a day administered intranasally, alternating nostrils daily into one nostril only. You should switch between each nostril every time you use Sandoz Calcitonin NS. Your physician may prescribe calcium and vitamin D together with Sandoz Calcitonin NS to help retard the progressive loss of bone mass. Please see the instructions below on how to prepare the spray bottle.

Use in pregnancy and breast feeding.
Do not take Sandoz Calcitonin NS if you are pregnant or breast feeding.

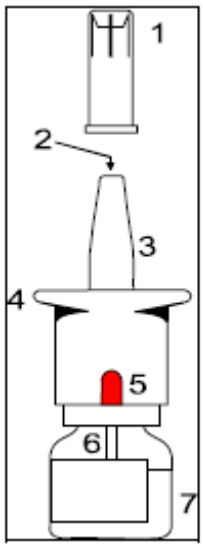
Use in children
Sandoz Calcitonin NS is not indicated for children under 18 years of age and should not be given to them.

Use in elderly
Sandoz Calcitonin NS works equally well in and is equally well tolerated by patients older and younger than 65 years of age.

Instructions for use/handling of Sandoz Calcitonin NS Nasal Spray

Please read the instructions carefully so that you know how to use your nasal spray.
• If the spray mechanism should become blocked, this may be resolved by pressing down firmly on the pump; do not attempt to unblock it by using a sharp pointed object as this may cause damage. If you think your nasal spray is not working properly, take it back to your pharmacist. **Never** try to fix the nasal spray yourself or take it apart, as this may affect your dose.
• Always follow your doctor's instructions regarding dosage carefully.
• Keep this leaflet in a safe place so that you can read it again.

The different parts of your nasal spray



1. **Protective cap**: Keeps the nozzle clean and protects the jet. Always replace the protective cap after you have used the nasal spray.

2. **Jet**: The tiny hole from which the solution sprays out.

3. **Nozzle**: The part you insert into your nostril.

4. **Pump**: The part you press down to operate the spray.

5. **Counter**: The dose counter window on a new nasal spray shows , as shown in this picture. The display will change as you use the pump (see below).

6. **Dip tube**: The tube inside the spray bottle that draws up the solution when you press the pump.

7. Bottle: Contains enough solution for at least 14 doses.

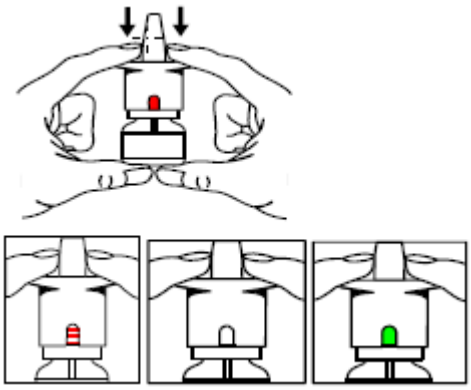
How to Prepare Sandoz Calcitonin NS Nasal Spray

Upon starting each new bottle of Sandoz Calcitonin NS, you must prime the pump (step 2). You should allow the bottle to reach room temperature before priming the pump. Once the bottle has been opened and primed, you do not need to repeat step 2 for the remainder of the time you use the bottle (approximately 14 sprays).

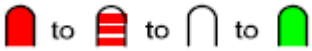
NEVER shake the nasal spray bottle as this could cause air bubbles, which may affect your dose. The dose counter window of a new nasal spray bottle is in the position marked as shown in the picture

1Remove the protective cap.

2 **First time of use only:**
Hold the nasal spray upright in one or two hands and press down firmly on the pump **3 times**.
This primes the new spray by clearing air out of the dip tube. You will only need to do this once when you start a new spray.
Do not worry if a little solution sprays out; this is normal.



As you press the pump, watch the changes in the dose counter window.



When green is showing in the dose counter window, your new nasal spray is ready to use. Follow the instructions for 'Using your nasal spray.

Using the nasal spray

1. With the protective cap removed, bend your head slightly forward and insert the applicator nozzle into one of your nostrils. Make sure it is in a straight line with the nasal passage to allow the spray mist to spread more evenly. Depress the plunger once and release (see drawing). In the counter window you will now see the number 1.

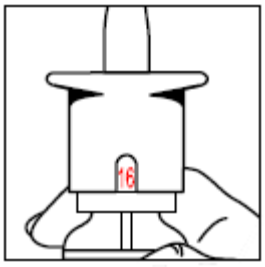
2 . After taking a dose, sniff vigorously several times to prevent the solution from running out of your nose. Do not blow your nose immediately after taking a dose.

3. After use, clean the nozzle with a dry tissue and always replace the protective cap to prevent the jet from becoming blocked.

4. Checking the counter: Every time you use the nasal spray the number in the dose counter window will change. The number displayed tells you how many puffs you have already taken. The Nasal Spray is guaranteed to deliver 14 metered doses. You may be able to obtain 2 extra doses.

When the dose counter window shows a red 

as shown in this picture, 16 puffs have been used and the nasal spray is finished. You may notice that a little liquid is left in the nasal spray bottle, but this is normal.



5. Under no circumstances attempt to enlarge the jet with a needle or sharp object. This will destroy the function completely. Do not dismantle the pump. To ensure even dosage, store or carry the bottle in an upright position. Avoid shaking and extremes of temperature.

6. Once opened, the nasal spray bottle must be kept at room temperature and used for a maximum of 4 weeks

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget your dose of Sandoz Calcitonin NS, do not double your dose at the next use

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Sandoz Calcitonin NS, as with any medicine, may have side effects.
The most commonly reported adverse events with Sandoz Calcitonin NS Nasal Spray are local effects such as sore nose, runny and stuffy nose (rhinitis), nasal dryness with crusting, non-severe epistaxis,

inflammation of the sinuses (feeling of pressure or pain in nose, cheeks and behind eyes), sneezing, nasal allergy, irritated nose, nasal odour, swelling, redness and damage of the mucus lining of the nose.

Rarely, patients may experience nausea, vomiting or dizziness. These effects usually disappear on their own.

Sandoz Calcitonin NS may cause fatigue, dizziness and disturbed vision, which may impair your reactions. If this happens, you should not drive or use machines.

Tell your doctor or pharmacist if you have any side effect not mentioned in this leaflet, or if any of the side effect mentioned above persists or becomes bothersome.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist immediately
		Only if severe	In all cases	
Very rare	**Severe allergic reaction** possibly resulting hives, rapid heartbeat, breathing difficulties, a feeling of swelling in the throat or tightness in chest.			√
	Sudden **life-threatening allergic reaction** leading to events such as a fall in blood pressure and sometimes shock.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist immediately
		Only if severe	In all cases	
Uncommon	Swelling of your face, limbs or entire body.			√

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Calcitonin NS, contact your doctor or pharmacist.

HOW TO STORE IT

Unopened Sandoz Calcitonin NS Nasal Spray should be stored in the refrigerator between 2 and 8°C and protected from freezing.

• After priming, Sandoz Calcitonin NS Nasal Spray should be stored at room temperature (between 15-30°C) and used within 4 weeks.

• To ensure correct delivery, the bottle should be kept in an upright position at all time to reduce the risk of air bubbles getting into the dip tube.
Store in the original package.

• Do not use this medicine after the expiry date printed on the label.

• Remember to keep Sandoz Calcitonin NS and all medications out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associat with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and :**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect ™ Canada site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Sandoz Canada Inc., at:
1-800-361-3062
or
by written request at:
145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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