PRODUCT MONOGRAPH

[PR] PRO-CALCITONIN -200

Calcitonin (Salmon) Nasal Solution

200 IU / spray

Bone Metabolism Regulator

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PRODUCT MONOGRAPH

PrPRO-CALCITONIN - 200

Calcitonin (Salmon) Nasal Solution

200 IU / spray

THERAPEUTIC CLASSIFICATION

Bone Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

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).

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. Calcitonin (salmon) nasal solution 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, calcitonin (salmon) nasal solution is more potent and longer acting. In terms of bioactivity, the potency of calcitonin (salmon) nasal solution 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.

Calcitonin (salmon) nasal solution 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. Calcitonin (salmon) nasal solution 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.

Calcitonin (salmon) nasal solution has also been shown to be successful in reducing pain associated with osteolytic and osteopenic conditions, probably by action on the central nervous system.

Pharmacokinetics

The data on bioavailability of calcitonin (salmon) nasal solution 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. Calcitonin (salmon) nasal solution is absorbed rapidly by the nasal mucosa. Maximum plasma concentrations occur within the first hour of administration. 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 half-life of elimination of salmon calcitonin is calculated to be about 45 minutes. There is no accumulation of the drug on repeated administration at 10-hour intervals for up to 15 days.

INDICATIONS AND CLINICAL USE

PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) is indicated for the treatment of postmenopausal osteoporosis in females greater than five years postmenopause

with low bone mass relative to healthy premenopausal females. PRO-CALCITONIN Nasal Spray should be reserved for patients who refuse or cannot tolerate treatment with estrogens or in whom estrogens are contraindicated. PRO-CALCITONIN Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 IU per day) intake to retard the progressive loss of bone mass.

CONTRAINDICATIONS

Known hypersensitivity to salmon calcitonin or to any component of the formulation (see WARNINGS and ADVERSE REACTIONS sections.)

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. In clinical trials with calcitonin (salmon) nasal solution, no serious allergic-type adverse reactions have been reported. However, in foreign marketing experience, 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. The usual provisions should be made for the emergency treatment of such a reaction should it occur. For patients with a history of hypersensitivity, emergency self-injection therapy should be considered. Allergic reactions should be differentiated from generalized flushing and hypotension.

Skin testing should be considered prior to treatment with calcitonin (salmon) nasal solution 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.

PRECAUTIONS

Nasal Examinations

Nasal adverse events were the most frequently reported adverse event, occurring in 17% of patients who received calcitonin (salmon) nasal solution and in 14% of patients who received placebo nasal solution 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 calcitonin (salmon) nasal solution, the most commonly reported nasal adverse events included rhinitis (8.2%), nasal dryness (3.9%), epistaxis (2.4%), and sinusitis (1.6%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. 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 solution should be discontinued. Although smaller ulcers often heal without withdrawal of calcitonin (salmon) nasal solution, medication should be discontinued temporarily until healing occurs.

Pregnancy

Synthetic calcitonin (salmon) 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) does not cross the placental barrier, this may be due to metabolic effects in the pregnant animal. There are no adequate and well controlled studies in pregnant women with s-calcitonin. Calcitonin (salmon) nasal solution is not indicated in pregnancy.

Nursing Mothers

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

Children

The safety and efficacy of calcitonin (salmon) nasal solution in children have not been established. 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 with this disorder is very limited.

Use in the Elderly

Clinical trials using calcitonin (salmon) nasal solution 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.

Laboratory Tests

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin (salmon) nasal solution. 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 calcitonin (salmon) nasal solution on immobilization osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after salmon calcitonin therapy was stopped.

Instructions for the Patient

Instructions on priming of the pump upon first use of the device and nasal introduction of calcitonin (salmon) nasal solution 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:

- Store new, unopened bottles in the refrigerator between 2-8°C.
- Protect the product from freezing.
- 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.

Drug Interactions

Formal studies designed to evaluate drug interactions with s-calcitonin have not been conducted. Currently no drug interactions with synthetic calcitonin (salmon) have been observed.

ADVERSE REACTIONS

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

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

Calcitonin (salmon) nasal solution was rarely associated with systemic effects, such as nausea, vomiting, dizziness, flushing accompanied by a sensation of heat and, uncommonly, polyuria and chills. These effects usually subsided spontaneously. Such systemic adverse events occur less frequently following intranasal administration of calcitonin (salmon) nasal solution than following i.v., i.m. or s.c. administration.

In very rare cases, calcitonin (salmon) nasal solution may give rise to hypersensitivity reactions such as generalized skin reactions. Isolated anaphylactic-type reactions including tachycardia, hypotension and collapse have been reported in post-marketing experience.

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.

The following table is based on controlled trials in patients treated with calcitonin (salmon) nasal solution 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 calcitonin (salmon) nasal solution all combined doses treatment group, irrespective of causal relationship to study drug.

Body System/Adverse Event	Calcitonin (Salmon) Nasal Solution (n=697) %	Placebo (n=389) %
Respiratory System (Nasal/Non Nasal)		
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		
Abdominal pain	3.0	1.5
Constipation	1.7	1.8
Nausea	1.7	1.0
Dyspepsia	1.6	0.3
Body as a Whole		
Influenza symptoms	1.6	2.6
Fatigue	1.1	0.3
Cardiovascular		
Hypertension	1.7	0.8
CNS/Psychiatric		
Headache	2.7	2.8
Depression	1.6	1.5
Dizziness	1.6	0.8
Musculoskeletal		
Back pain	2.9	0.8
Arthralgia	2.0	1.8
Bone fracture	1.4	1.5
Arthrosis	1.0	1.0
Vision Disorder		
Lacrimation abnormal	1.0	0.8
Urinary		
Cystitis	1.1	1.0
Other		
Flushing	4.6	5.1
Infection	1.4	1.0

Calcitonin (salmon) nasal solution 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 calcitonin (salmon) nasal solution and 307 patients exposed to placebo nasal solution, 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 calcitonin (salmon) nasal solution and placebo groups.

In the P.R.O.O.F. trial, nasal adverse events assessed as definitely, probably, possibly, or unlikely drug related by the investigators included:

Nasal Adverse Event	Calcitonin (Salmon) Nasal Solution (n=942)%	Placebo (n=307)%
Rhinitis	30.6	20.8
Symptoms of the nose unspecified	15.8	13.0
Epistaxis	12.6	11.7
Rhinitis ulcerative	3.4	1.6

Less frequently reported nasal adverse events occurring in less than 1% of patients included nasal polyp, nasal septum ulceration, and nasoseptal deviation. Most of the nasal events were mild to moderate in severity and did not prompt discontinuation. Calcitonin (salmon) nasal solution nasal adverse event rates were 73.5% mild, 24.3% moderate, and 2.2% severe (placebo nasal solution adverse event rates were 69.5% mild, 24.3% moderate, and 6.2% severe).

In addition, during the P.R.O.O.F. trial, edema (e.g. tongue, extremity, face, generalized) occurred in 3.1% and 2.6% of patients who received calcitonin (salmon) nasal solution and placebo nasal solution, respectively. Allergy occurred in 1.6% and 1.4% of patients who received calcitonin (salmon) nasal solution and placebo nasal solutions, respectively.

Additional adverse reactions that occurred in the P.R.O.O.F. trial and not included in the 2 year trials data are: pain (i.e. musculoskeletal, general), arthropathy, hot flushes, accidental trauma, asthenia, chest pain, skin disorder (e.g. fissures, lesions, sores), dry skin, leg pain,

cramps, chest sounds abnormal (e.g. basilar, crepitations, rales), arrhythmia, hypercalcemia, dysphonia, somnolence, ear disorder (e.g. sensation of fullness, stuffiness, blockage), vision abnormal, cataract, eye abnormality (e.g. dryness, infection, irritation), glaucoma, purpura.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Single doses of calcitonin (salmon) nasal solution up to 1600 IU and doses up to 800 IU per day for three days and chronic administration of doses up to 600 IU per day have been studied without serious adverse effects. A dose of 1000 IU of synthetic calcitonin (salmon) injectable solution given subcutaneously may produce nausea and vomiting. A dose of synthetic calcitonin (salmon) injectable solution of 32 IU 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 calcitonin (salmon) nasal solution 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 PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) in postmenopausal women is one spray (200 IU) 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.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper/Common Name: Calcitonin (salmon)

Chemical Name: L-Cysteinyl-L-seryl-L-asparaginyl-L-leucyl-L-seryl-L-threonyl-L-cysteinyl-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-prolyl-L-arginyl-L-threonyl-L-asparaginyl-L-threonyl-glycyl-L-seryl-glycyl-L-threonyl-L-proline amide 3,7-3,1 disulfide

Structural Formula:

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2

Molecular Formula: $C_{145}H_{240}N_{44}O_{48}S_2$

Molecular Weight: 3431.9

Description:

It is a white or almost white powder. Freely soluble in water.

COMPOSITION

Each spray of PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) contains 200 IU of synthetic calcitonin (salmon) as the active ingredient and the following non-medicinal ingredients: Benzalkonium chloride (as a preservative), hydrochloric acid and/or sodium hydroxide (for pH adjustment), sodium chloride and purified water.

STABILITY AND STORAGE RECOMMENDATIONS

Unopened PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) should be stored in the refrigerator between 2 and 8°C and protected from freezing.

After priming, PRO-CALCITONIN Nasal Spray should be stored at room temperature (below 25°C) and used within 4 weeks. To ensure correct delivery, the bottle should be kept in an upright position.

AVAILABILITY OF DOSAGE FORMS

PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) is available in spray bottles delivering at least 14 metered doses of 200 International Units (IU), one unit corresponding to about 0.2 µg of synthetic calcitonin (salmon).

Each pack contains two (2) bottles of spray solution. The device is composed of a clear, uncoloured glass bottle (Type I glass) and a metered nasal spray pump with actuator and cap.

INFORMATION FOR THE PATIENT

PRO-CALCITONIN
Calcitonin (Salmon) Nasal Solution, 200 IU per spray

Before using PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution), please read this leaflet carefully because it contains important information about this medicine. If you have further questions, ask your doctor or pharmacist.

PRO-CALCITONIN 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 µg of synthetic calcitonin (salmon).

Your physician has prescribed PRO-CALCITONIN Nasal Spray to you because you have a disease known 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).

What does PRO-CALCITONIN Nasal Spray do?

Calcitonin (salmon) nasal solution has been shown to delay progressive bone loss in postmenopausal osteoporosis. PRO-CALCITONIN Nasal Spray not only delays the loss of bone but actually helps to rebuild bone you may have lost and makes bone less likely to fracture. In addition, your physician may recommend one or more of the following lifestyle changes:

- **Stop smoking.** Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of fracture.
- **Exercise.** Like muscles, bones need exercise to stay strong and healthy. Consult your physician before you begin any exercise program.
- **Eat a balanced diet.** Your physician can advise you whether to modify your diet or to take any dietary supplements.

SOME GUIDELINES FOR USING PRO-CALCITONIN Nasal Spray

What is the dose of PRO-CALCITONIN Nasal Spray?

The recommended dose of PRO-CALCITONIN Nasal Spray (Calcitonin [Salmon] Nasal Solution) is one spray (200 IU) per day administered intranasally (by way of the nose), alternating nostrils daily. Your physician may prescribe calcium and vitamin D together with PRO-CALCITONIN Nasal Spray to help retard the progressive loss of bone mass. Please see the instructions below on how to prepare the spray bottle.

What if I miss a dose?

Take PRO-CALCITONIN Nasal Spray once daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule of one spray per day.

How to Prepare PRO-CALCITONIN Nasal Spray

Upon starting each new bottle of PRO-CALCITONIN Nasal Spray, 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).

1. Remove the clear plastic dust cap and the blue safety clip from the nasal spray pump (Figure 1). The safety clip prevents the accidental discharge of the spray in your pocket or purse.

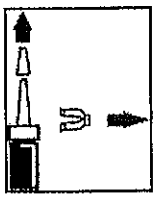

Figure 1

2. **First time of use only:** To ensure a proper delivery of medication, a newly opened bottle must be primed before you use it for the first time. Holding the bottle upright with your index and middle fingers on the two shoulder areas of the pump, and your thumb on the bottom of the bottle, press the shoulders down fully, then release (Figure 2). Do this three times. Now the nasal spray is ready for use.

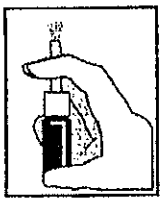

Figure 2

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

3. 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 (Figure 3).

Figure 3

4. 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.

5. Always replace the blue safety clip and the protective cap to prevent the jet from becoming blocked (Figure 4). Be careful not to depress the pump while this is being done.

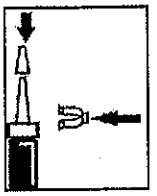

Figure 4

6. 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.

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

Why is it important to continue to take PRO-CALCITONIN Nasal Spray?

It is important to take PRO-CALCITONIN Nasal Spray over the long-term to continue to delay loss of bone and to help rebuild bone you may have lost. It is, therefore, important to follow your physician's instructions for taking PRO-CALCITONIN Nasal Spray without skipping doses or varying from your prescribed treatment schedule. It is also important to continue to follow your physician's advice on lifestyle changes.

Who should not take PRO-CALCITONIN Nasal Spray?

You should not take PRO-CALCITONIN Nasal Spray if you are allergic to salmon calcitonin or to any component of the formulation (see list of ingredients below).

What should I tell my physician or pharmacist before taking PRO-CALCITONIN Nasal Spray?

Tell your physician or pharmacist about any medical problems you have or have had, including chronic rhinitis (chronic inflammation of the mucous membranes of the nose) and about any allergies.

Use in Pregnancy and Breast Feeding

Do not take PRO-CALCITONIN Nasal Spray if you are pregnant or breast feeding.

Use in Children

PRO-CALCITONIN Nasal Spray is not indicated for children and should not be given to them.

Use in Elderly

PRO-CALCITONIN Nasal Spray works equally well in and is equally well tolerated by patients older and younger than 65 years of age.

Can I drive or operate machinery while using PRO-CALCITONIN Nasal Spray?

PRO-CALCITONIN Nasal Spray should not affect your ability to drive or operate machinery.

What side effects can PRO-CALCITONIN Nasal Spray have?

Most patients do not have side effects from calcitonin (salmon) nasal solution, however, as with any medicine, calcitonin (salmon) nasal solution may have unintended or undesirable effects. Side effects usually have been mild. The most commonly reported adverse events with calcitonin (salmon) nasal solution are local effects such as rhinitis (inflammation of the mucous membranes of the nose), nasal dryness with crusting, non-severe epistaxis (nosebleed) and sinusitis. Rarely, patients may experience nausea, vomiting or dizziness. These effects usually disappear on their own.

Your physician or pharmacist has a more complete list. Tell your physician or pharmacist promptly about these or any other unusual symptoms.

How long should I keep my medicine?

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

Important Points to Remember

Remember to keep PRO-CALCITONIN Nasal Spray and all medications safely away from children.

Storage

Unopened PRO-CALCITONIN Nasal Spray should be stored in the refrigerator between 2 and 8°C and protected from freezing.

After priming, PRO-CALCITONIN Nasal Spray should be stored at room temperature (below 25°C) and used within 4 weeks. To ensure correct delivery, the bottle should be kept in an upright position.

Product Ingredients

Each spray contains 200 IU of synthetic calcitonin (salmon) as the active ingredient and the following non-medicinal ingredients: Benzalkonium chloride (as a preservative), hydrochloric acid and/or sodium hydroxide (for pH adjustment), sodium chloride and purified water.

PHARMACOLOGY

Summary of Major Points from Experimental Studies

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).

Because of its chemical nature (a peptide of 32 amino acids), calcitonin is usually 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.

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, Mill Hill, London. Recently an official standard has been prepared (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.

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.

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 parathyroid 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.

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. 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.

Human Studies Pharmacokinetics

The absolute bioavailability of synthetic calcitonin (salmon) is about 70% after either intramuscular or subcutaneous injection. Maximal plasma concentrations are obtained within one hour. 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%. The apparent volume of distribution is 0.15 - 0.3 L/kg, and protein binding amounts to 30-40%.

The data on bioavailability of calcitonin (salmon) nasal solution 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 synthetic calcitonin (salmon) are not predictive of the therapeutic response, and hence s-calcitonin activity should be evaluated by biochemical or clinical parameters. Calcitonin (salmon) nasal solution is absorbed rapidly by the nasal mucosa. Maximum plasma concentrations occur within the first hour of administration. 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 half-life of elimination of synthetic calcitonin (salmon) is calculated to be about 45 minutes. There is no accumulation of the drug on repeated administration at 10-hour intervals for up to 15 days.

Clinical Experience

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.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with PTH in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. A reduction in the transfer of calcium from bone to blood results and blood calcium tends to return to 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 normal children and in patients with generalized Paget's disease, bone resorption is more rapid and decreases in serum calcium are more pronounced in response to calcitonin.

Treatment of Osteoporosis in Postmenopausal Women

Effect on Bone Mineral Density

Two randomized placebo controlled trials were conducted in 325 postmenopausal females [227 calcitonin (salmon) nasal solution 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 IU daily of calcitonin (salmon) nasal solution increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 year postmenopause. Calcitonin (salmon) nasal solution 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 calcitonin (salmon) nasal solution 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

The Prevent Recurrence of Osteoporotic Fractures Trial (P.R.O.O.F.) was a 5 year study which included results from 1255 patients who were at least 1 year postmenopausal with a lumbar spine BMD of at lease 2 standard deviations below the mean for young adult females, and at lease 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 IU vitamin D. 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 calcitonin (salmon) nasal solution 200 IU daily as compared to placebo. The risk of new vertebral fractures was 36% ($p=0.020$) lower in the calcitonin (salmon) nasal solution 200 IU/day group compared to placebo. Calcitonin (salmon) nasal solution reduced the risk of new and/or worsening vertebral fractures by 28% ($p=0.064$) compared to placebo. In addition, calcitonin (salmon) nasal solution 200 IU/day reduced the proportion of patients experiencing multiple incident new and/or worsening vertebral fractures by 35% (25/286 in the 200 IU 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 calcitonin (salmon) nasal solution (doses ranging from 50 IU to 200 IU daily) compared with those who received placebo.

Circulating antibodies to salmon calcitonin after up to 60 months of treatment with calcitonin (salmon) nasal solution 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.

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 calcitonin (salmon) nasal solution.

Analgesia

Clinical studies demonstrate that salmon calcitonin possesses analgesic activity. Specific salmon calcitonin binding sites were found in some areas of the central nervous system.

TOXICOLOGY

Synthetic calcitonin (salmon) 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 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 calcitonin (salmon) nasal solution was assessed in the cynomolgus monkey following intranasal administration of 0 (control), 400, 800, and 1600 IU/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 calcitonin (salmon) nasal solution was tolerated in the monkey at dosages up to 1600 IU/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 IU) 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 IU) 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 IU/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 conjunctiva 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 proliferatiing 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.

REFERENCES

1) Accardo G, Aleotti A, Ricci D, Pazza A. Support for the clinical use of calcitonin: electron microscope study of the functional state of bone cells of rats after chronic treatment with calcitonin. Curr Ther Res 1982; 31: 422-433.

2) Buclin T, Randin JP, Jacquet AF, Azria M, Attinger M, Gomez F, Burckhardt P. The effect of rectal and nasal administration of salmon calcitonin in normal subjects. Calcif Tissue Int 1987; 41: 252-258.

3) Christiansen C, Riis BJ, Hohansen JS et al. The effect of nasal calcitonin on postmenopausal osteoporosis. Int Symp on Osteoporosis 1987; Sept. 27 - Oct 2.

4) Copp DH et al. Evidence for calcitonin. A new hormone from the parathyroid that lowers blood calcium. Endocrinology 1962; 70: 638.

5) Copp DH et al. Calcitonin and ultimobranchial function of lower vertebrates. Calcitonin 1969. Proceedings of the Second International Symposium; William Heinemann Medical Books Ltd, London 1970; pp. 281.

6) DeVernejoul MC, Pointillart A, Bourdeau A, Morieux C, Modrowski D, Miravet L, Caulin F. Effect of calcitonin administration on young pig trabecular bone remodelling. Bone 1990; 11:29-33.

7) Doepfner WEH. Pharmacological effects of calcitonin. Triangle 1983; 22: 57-67.

8) Fournié A, Valverde C, Tap G, Bazerque J-J, Ayrolles C. Test d'hypocalcémie aiguë à la calcitonine de proc et de saumon. Rev Rhum 1977; 44: 91-98

9) Gennari C. Clinical aspects of calcitonin in pain. Triangle 1983; 22: 156-163.

10) Gennari C, Gonnelli S, Chierichetti SM, Piolini M, Francini G, Montagnani M, Marbach P. Antibody problem in calcitonin administration. IN: Calcitonin 1984: Chemistry, Physiology, Pharmacology and Clinical Aspects. A Pecile ed, Excerpta Medica, Amsterdam 1985; pp. 457-468.

11) Geusens P, Boonen S, Nijs J, Jiang Y, Lowet G, VanAuderkercke R, Huyghe C, Caulin F, Very JM, Dequeker J, VanderPerre G. Effect of salmon calcitonin on femoral bone quality in adult ovariectomised ewes. Calcif Tissue Int 1996; 59: 315-320.

12) Goltzman D, Mitchell J. Calcitonin and calcitonin gene-related peptide: analysis of discrete and overlapping interactions at receptor sites. IN: Calcitonin 1984: Chemistry, Physiology, Pharmacology and Clinical Aspects. A Pecile ed, Excerpta Medica, Amsterdam 1985; pp. 245-252.

13) Gruber HE, Ivey JL et al. Long-term calcitonin therapy in postmenopausal osteoporosis. Metabolism 1984; 33: 295-303.

14) Guttman S et al. Synthesis of salmon calcitonin, a highly active hypocalcemic hormone. Helv Chim Acta 1969; 52: 1789.

15) Hartman DA et al. Abnormal urinary sediment during therapy with synthetic salmon calcitonin. J Clin Endocr 1971; 33: 564.

16) Hywyler R, Born W, OhnHaus EE. Plasma kinetics and urinary excretion of exogenous human and salmon calcitonin in man. Amer J of Physioloy 1979; 239(1): E15-E19.

17) Ichikawa, Masaki, Nakamuta, Hiromichi, Hoshino, Takashi, Ogawa, Yasunao, Masao Koida. Anti-osteopenic effect of nasal salmon calcitonin in Type 1 osteoporotic rats: Comparison with subcutaneous dosing. Biol Pharm Bull 1994; 17(7): 911-913.

18) Kurose H, Seino Y, Shima M, Tanaka H, Ishida M, Yamaoka K, Yabuuchi H. Intranasal absorption of salmon calcitonin. Calcif Tissue Int 1987; 41: 249-251.

19) Li M, Shen Y, Buron KW, DeLuca PP, Mehta RC, Baumann BD, Wronski TJ. A comparison of the skeletal effects of intermittent and continuous administration of calcitonin in ovariectomised rats. 1996; 18(4): 375-380.

20) MacIntyre I, Stevenson JC et al. Calcitonin for prevention of postmenopausal bone loss. Lancet 1988; ii: 1481-1483.

21) Mosekilde L. Assessing bone quality: Animal models in preclinical osteoporosis research. Bone 1995; 17(4 Suppl): 343S-352S.

22) Mosekilde, Lis, Danielsen, Christian C, Gasser J. The effect on vertebral bone mass and strength of long term treatment with antiresorptive agents (estrogen and calcitonin), human parathyroid hormone (1-38) and combination therapy, assessed in aged ovariectomised rats. Endocrinol 1994; 134(5): 2126-2134.

23) Niall HD et al. Amino acid sequence of salmon ultimobranchial calcitonin. Proc Nat Acad Sci 1969; 64: 771.

24) Nuesch E, Schmidt R. Comparative pharmacokinetics of calcitonins. IN: Calcitonin 1980: Chemistry, Physiology, Pharmacology and Clinical Aspects. A. Pecile ed, Excerpta Medica, Amsterdam 1981; pp. 352-364.

25) Overgaard K, Riis BJ, Christiansen C et al. Effect of calcitonin given intranasally on early postmenopausal bone loss. Br Med J 1989; 299:477.

26) Paillard F et al. Renal effects of salmon calcitonin in man. J Lab Clin Med 1972; 80(2): 200.

27) Parkes CO et al. Purification of calcitonin from salmon ultimobranchial glands. Fed Proc 1969; 28: 413.

28) Reginster JY, Albert A, Lecart MP, Lambelin P, Denis D, Deriosy R, Fontaine MA, Franchimont P. One-year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. Lancet 1987; 8574: 1481-1483.

29) Reginster JY, Deroisy R, Denis D, Lecart MP, Sarlet N, Franchimont P. Is there any place for salmon calcitonin in prevention of postmenopausal bone loss? Gynecol. Endocrinol 1988; 2: 195-204.

30) Reginster JY, Denis D, Albert A. First Biochemical and clinical results on the use of nasal salmon calcitonin in the prevention of postmenopausal osteoporosis. Int Symp on Osteoporosis 1987; Sept 27 - Oct 2.

31) Riggs BL. A new option for treating osteoporosis. New Eng J Med 1990; 323: 124-125.

32) Shen Y, Li M, Wronski TJ. Calcitonin provides complete protection against cancellous bone lose in the femoral neck of ovariectomised rats. Calcif Tissue Int 1997; 60; 457-461.

33) Stock J, Avioli LV, Baylink DJ et al. For the PROOF Study Group. A multicentered, double-blind, randomised study to investigate the efficacy of Miacalcin (calcitonin-salmon) nasal spray in reducing the incidence of new vertebral fractures: three-year results (Abstract). American Soc of Bone Mineral Research Meeting. 1997; Sept 10-Sept.

34) Thamsborg G, Storm TL, Brinch E et al. The effect of different doses of nasal salmon calcitonin on plasma cyclic AMP and serum calcium. Calcif Tiss Int 1990; 46: 5-8.

35) Thamsborg G, Storm TL, Sykulski R et al. Effect of different doses of nasal calcitonin on bone mass. Calcif Tiss Int 1991; 48: 302-307.

36) Thamsborg G, Storm TL, Sykulski R et al. Treatment with intranasal salmon calcitonin increases bone mass in postmenopausal females (Abstract). 1988; World congress of Gynecology and Obstetrics (Oct).

37) Toccafondi R, Brandi ML, Mavilla C, Zonefrati R. Biological effects of salmon calcitonin in osteoblast-like cells. IN: Calcitonin 1984: Chemistry, Physiology, Pharmacology and Clinical Aspects. A. Pecile ed, Excerpta Medica, Amsterdam 1985; pp. 197-204.

38) Wallach, Stanley, Farley, John R, Baylink, David, J, Leona Brenner-Gati. Effects of calcitonin on bone quality and osteoblastic function. Calcif Tissue Int 1993; 52: 335-339.

39) Wronski TJ, Yen CF, Buron KW, Mehta RC, Newman PS, Soltis EE and DeLuca PP. Skeletal effects of calcitonin in ovariectomised rats. Endocrinol 1991; 129(4): 2246-2250.

40) Zanussi C, Marini U, Rossi Ferinni P L, Scaltrini G, Visca U, Motta P, Piolini M. Calcitonin in multiple myeloma: a double-blind controlled clinical trial. IN: Calcitonin, 1984: Chemistry, Physiology, Pharmacology and Clinical Aspects. A. Pecile, ed., Excerpta Medica, Amsterdam 1985; pp. 379-388

41) Ziegler R. Calcitonin: analgesic effects. Cancer Res 1984; 89: 178-184.

42) Product Monograph. Miacalcin® NS Synthetic Calcitonin (Salmon) Nasal Spray, 200 IU/actuation. Bone Metabolism Regulator. Novartis Pharm. Canada Inc., August 26, 1999.

43) Prescribing Information. Miacalcin® NS Synthetic Calcitonin (Salmon) Nasal Spray, 200 IU/actuation. Bone Metabolism Regulator. Novartis Pharm. Canada Inc., Date of Revision: August 1, 2000.