CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-313/S-023

Trade Name: Miacalcin Nasal Spray

Generic Name: salmon calcitonin

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: August 22, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-313/S-023

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-313/S-023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-313/S-023

Novartis Pharmaceuticals Corporation
Attention: Joan Materna
Senior Associate Director, CMC
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Materna:

Please refer to your supplemental new drug applications dated April 21, 2003, received April 23, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miacalcin (salmon calcitonin) Nasal Spray.

This supplemental new drug application proposes a larger 7 mL vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses, and minor changes to analytical testing.

We have completed the review of this application. This application is approved, effective on the date of this letter for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the submitted draft labeling (vial label, vial carton, patient assembly instructions - patient package insert, and package insert submitted April 21, 2003).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-313/S-023." Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html. To expedite review of this patent declaration form, we request you submit an additional copy of the form to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Mamta Gautam-Basak, Ph.D.
Chemistry Team Leader II for the
Division of Metabolic and Endocrine Drug Products, (HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mamta Gautam-Basak
8/22/03 11:42:50 AM
Approved

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-313/S-023

APPROVED LABELING

NOVARTIS

Miacalcin®

(calcitonin-salmon)
Nasal Spray

T2006-43

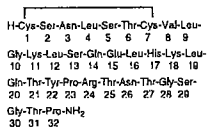
Rx Only

Prescribing Information

DESCRIPTION

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

Miacalcin® (calcitonin-salmon) Nasal Spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in a 3.7 mL fill glass bottle as a solution for nasal administration. This is sufficient medication for at least 30 doses.

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

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

The activity of Miacalcin Nasal Spray is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

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

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

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

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from the *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

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

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

Postmenopausal Osteoporosis

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

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

Calcium Homeostasis

In two clinical studies designed to evaluate the pharmacodynamic response to Miacalcin® Nasal Spray, administration of 100-1600 I.U. to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 I.U. did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney

Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with Miacalcin Nasal Spray.

Gastrointestinal Tract

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

Pharmacokinetics and Metabolism

The data on bioavailability of Miacalcin® Nasal Spray obtained by various investigators using different methods show great variability. Miacalcin® Nasal Spray is absorbed rapidly by the nasal mucosa. Peak plasma concentrations of drug appear 31-39 minutes after nasal administration compared to 16-25 minutes following parenteral dosing. In normal volunteers approximately 3% (range 0.3%-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by intramuscular injection. The half-life of elimination of calcitonin-salmon is calculated to be 43 minutes. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of nasally administered calcitonin has not been studied in postmenopausal women.

INDICATION AND USAGE

Postmenopausal Osteoporosis

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

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females (227 Miacalcin Nasal Spray treated and 98 placebo treated) with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 I.U. daily of Miacalcin Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Miacalcin 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 Miacalcin 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.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

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

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

PRECAUTIONS

Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Miacalcin® (calcitonin-salmon) Nasal Spray ingredients.

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

Periodic Nasal Examinations

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

The development of mucosal alterations or transient nasal conditions occurred in up to 9% of patients who received Miacalcin Nasal Spray and in up to 12% of patients who received placebo nasal spray in studies in postmenopausal females. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

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

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

Information for Patients

Careful instructions on pump assembly, priming of the pump and nasal introduction of Miacalcin Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 2°C-8°C (36°F-46°F).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.
- See DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump for complete instructions on priming the pump and administering Miacalcin Nasal Spray.

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

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

Carcinogenicity, Mutagenicity, and Impairment of Fertility

An increased incidence of non-functioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 I.U. per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area). The findings suggest that calcitonin-salmon reduced the latency period for development of pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon was tested for mutagenicity using *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in mammalian V79 cells of the Chinese Hamster *in vitro*.

Laboratory Tests

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with Miacalcin® Nasal Spray. Coarse granular casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered.

Pregnancy

Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well controlled studies in pregnant women with calcitonin-salmon. Miacalcin Nasal Spray is *not* indicated for use in pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

Pediatric Use

There are no data to support the use of Miacalcin® Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

Geriatric Use

In one large multicenter, double-blind, randomized clinical study of Miacalcin Nasal Spray, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old and 196 patients were 75 and over. Compared to subjects less than 65 years old, the incidence of nasal adverse events (rhinitis, irritation, erythema, and excoriation) was higher in patients over the age of 65, particularly those over the age of 75. Most events were mild in intensity. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Miacalcin®
(calcitonin-salmon)
Nasal Spray

ADVERSE REACTIONS
The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to Miacalcin® (calcitonin-salmon) Nasal Spray (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of Miacalcin Nasal Spray-treated patients are presented below in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

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

	Miacalcin® (calcitonin-salmon) Nasal Spray N=341	Placebo N=131
Adverse Reaction	% of Patients	% of Patients
Rhinitis	12.0	6.9
Symptom of Nose†	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with Miacalcin® Nasal Spray. Adverse events reported in 1%-3% of patients are identified with an asterisk(*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to Miacalcin® Nasal Spray has not been established.

Body as a Whole – General Disorders: influenza-like symptoms*, fatigue*, periorbital edema, fever

Integumentary: erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, parosmia

Cardiovascular: hypertension*, angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction

Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, flatulence, increased appetite, gastritis, dry mouth

Liver/Metabolic: cholelithiasis, hepatitis, thirst, weight increase

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation

Hearing/Vestibular: tinnitus, hearing loss, earache

Vision: abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater

Vascular: flushing, cerebrovascular accident, thrombophlebitis

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

Psychiatric: depression*, insomnia, anxiety, anorexia

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with Miacalcin Nasal Spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2%-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3%-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with Miacalcin Nasal Spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE
No instances of overdose with Miacalcin® (calcitonin-salmon) Nasal Spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of Miacalcin Nasal Spray up to 1600 I.U., 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 Miacalcin injectable solution given subcutaneously may produce nausea and vomiting. A dose of Miacalcin 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 Miacalcin Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION
The recommended dose of Miacalcin® (calcitonin-salmon) Nasal Spray in postmenopausal osteoporotic females is one spray (200 I.U.) per day administered intranasally, alternating nostrils daily.

Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of Miacalcin Nasal Spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to Miacalcin Nasal Spray therapy in these patients.

Priming (Activation) of Pump
Before the first dose and administration, Miacalcin Nasal Spray should be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position, and the pump firmly depressed toward the bottle. The pump should not be primed before each daily dose.

HOW SUPPLIED
Miacalcin® (calcitonin-salmon) Nasal Spray
Available as a metered dose clear solution in a 3.7 mL fill clear glass bottle. It is available in a dosage strength of 200 I.U. per activation (0.09 mL per spray). A screw-on pump is provided. The pump, following priming, will deliver 0.09 mL of solution. Miacalcin® Nasal Spray contains 2200 I.U. per mL calcitonin-salmon and is provided in an individual box containing one glass bottle and one screw-on pump .....NDC 0078-0311-54

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

Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

NOVARTIS

Manufactured by:
Novartis Pharma S.A.S.
Huningue, France

Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, New Jersey 07936

REV: JUNE 2006 PRINTED IN U.S.A. T2006-43 5000815


PMS 314
PMS 179
PMS 138
PMS 272
PMS 327
PMS 272 from 0% to 40%
NOVARTIS
Miacalcin
NASAL SPRAY
(calcitonin-salmon) Nasal Solution
200 I.U. per actuation
Active Ingredient:
calcitonin-salmon,
2200 I.U. per mL
(corresponding to 200 I.U.
per 0.09 mL actuation).
Inactive Ingredients:
sodium chloride,
benzalkonium chloride,
hydrochloric acid (added
as necessary to adjust pH)
and purified water.
Manufactured by:
Novartis Pharma S.A.S.
Huningue, France
Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936
0078-0311-54
NDC 0078-0311-54
3.7 mL bottle & applicator
30 dose bottle
200 I.U. calcitonin-salmon per actuation
FOR INTRANASAL USE ONLY
REFRIGERATE UNTIL OPENED
Rx only
3.7 mL bottle
Dose Recommendation:
One 200 I.U. spray per day.
See package insert for further
dosage information, important
patient information enclosed.
Each spray will dispense 0.09 mL,
which will contain 200 I.U.
(one dose) of calcitonin-salmon.
Bottle contains at least 30 doses.
FOR INTRANASAL USE ONLY
Store bottle in use at room
temperature between 15°C-30°C
(59°F-86°F) for up to 35 days in
an upright position.
Store unopened bottle in
refrigerator between 2°C-8°C
(36°F-46°F) until ready to use.
Protect from freezing.

LOT

EXP.

NDC 0078-0311-54

Miacalcin®

NASAL SPRAY

(calcitonin-salmon) Nasal Solution

30 dose bottle 3.7 mL

200 I.U. per actuation **Rx only**

FOR INTRANASAL USE ONLY

Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.

Manufactured by:
Novartis Pharma S.A.
Huningue, France
©Novartis

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85059401

Information for the Patient

T2003-12
89019501

Miacalcin®

(calcitonin-salmon)

Nasal Spray

What is MIACALCIN® [MEE-uh-KAL-sin] Nasal Spray?

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

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

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

What is osteoporosis after menopause? What causes it?

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

Osteoporosis occurs most frequently in women who have gone through menopause. At menopause, a woman's body goes through many changes, including a substantial decrease in the amount of estrogen produced. Estrogen in your body helps keep bones strong – without it, they may become weak.

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

- Curved spine
- Rounded shoulders
- Loss of height

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

How does MIACALCIN® Nasal Spray work?

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

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

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

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

How do I use MIACALCIN® Nasal Spray?

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

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

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

Who should not take MIACALCIN® Nasal Spray?

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

You should be aware of these warnings and precautions when taking MIACALCIN® (calcitonin-salmon) Nasal Spray.

- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed with the use of MIACALCIN® Nasal Spray. You should inform your doctor and pharmacist about the other prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking MIACALCIN® Nasal Spray. For this reason, it is recommended that a nasal examination be performed prior to the start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with MIACALCIN® Nasal Spray. In some cases, your doctor may decide to temporarily discontinue treatment with MIACALCIN® Nasal Spray until symptoms subside.
- Because calcitonin-salmon is a protein, the possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use MIACALCIN® Nasal Spray.
- MIACALCIN® Nasal Spray is safe to use in elderly patients. No unusual side effects or increases in common side effects have been seen in patients over 65 years of age.

Possible side effects

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

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

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

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

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

89019501

Miacalcin® NASAL SPRAY
(calcitonin-salmon) Nasal Solution

Miacalcin® NASAL SPRAY
(calcitonin-salmon) Nasal Solution

89019501

NOVARTIS

Manufactured by:
Novartis Pharma S.A.S.
Huningue, France

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

REV: APRIL 2003 Printed in U.S.A.

T2003-12
89019501

HOW TO ASSEMBLE AND USE

Miacalcin®
NASAL SPRAY

(calcitonin-salmon) Nasal Solution

ONE SPRAY, ONCE A DAY

BEFORE USING MIACALCIN® (calcitonin-salmon) NASAL SPRAY

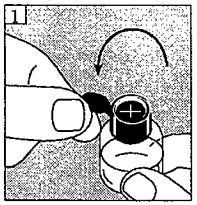
This package contains one bottle of MIACALCIN® (calcitonin-salmon) Nasal Spray and one screw-on pump.

Important Facts About Your Medication:

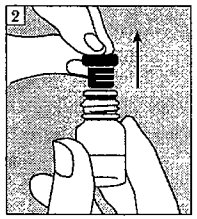
- The bottle contains the proper amount of medication — be aware that the entire bottle will not be filled with liquid.
- Before opening and assembling your medication bottle, keep it in your refrigerator between 2°C-8°C (36°F-46°F). Do not freeze.
- After opening and assembling a new medication bottle, keep it at room temperature between 15°C-30°C (59°F-86°F) in an upright position.

HOW TO USE MIACALCIN® (calcitonin-salmon) NASAL SPRAY

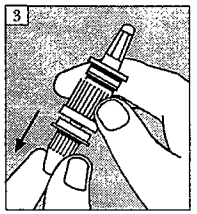
Putting the Nasal Spray Pump Unit Together



1. If your bottle and pump unit were already assembled by your pharmacist, go to step 6. If not, remove the bottle from your refrigerator and allow it to reach room temperature before assembling. Lift up the blue plastic tab and carefully pull the metal safety seal off the bottle.

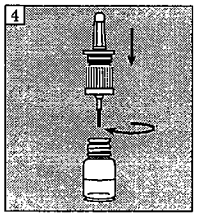


2. Keeping the bottle upright, remove the rubber stopper from the bottle.

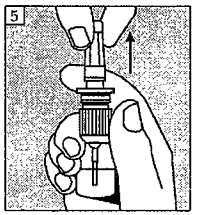


3. Holding the pump unit, gently remove the opaque plastic protective cap from the bottom of the unit.

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

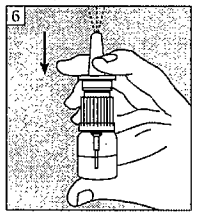


4. Holding the bottle upright, insert the nasal spray pump unit into the bottle. Then turn the pump clockwise, and tighten it until it is securely fastened to the bottle.



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

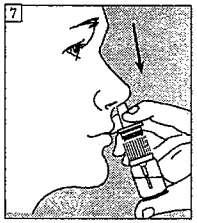
Priming a New Bottle



6. **To ensure proper delivery of medication, a newly opened and assembled bottle must be primed before you use it for the first time. If your pharmacist assembled the unit for you**, check to see if it has already been primed by pumping the unit once. If a full spray is emitted, the unit has already been primed. If no spray is emitted, you must prime the unit. Holding the bottle upright with your index and middle fingers on the two side arms of the pump, and your thumb on the bottom of the bottle, press the arms down fully **until you see a full spray**. Now the nasal spray is ready for use.

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

Using the Medication



7. The recommended dose of MIACALCIN® (calcitonin-salmon) Nasal Spray is one spray once a day in one nostril.

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

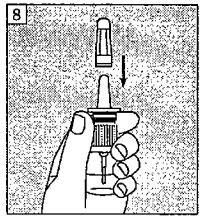
Tilt the bottle until it is in a straight line with the nasal passage.

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

Cleaning the Pump

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

Storing the Unit



8. Holding the bottle with two fingers **under** the two side arms of the pump, gently replace the protective cap on the nasal spray unit. **Be careful not to depress the pump** while this is being done. Once the pump is primed, the unit must be kept at room temperature between 15°C-30°C (59°F-86°F) in the upright position until the medication is finished.

IMPORTANT

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

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

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

Alternate Nostrils Daily

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

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

IMPORTANT

- **Use MIACALCIN® (calcitonin-salmon) Nasal Spray daily.**

To ensure proper treatment, it is important to use your MIACALCIN® (calcitonin-salmon) Nasal Spray daily even if you have no symptoms of postmenopausal osteoporosis.

What Is the Correct Dose of MIACALCIN® (calcitonin-salmon) Nasal Spray?

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

For more information on MIACALCIN® Nasal Spray and how to assemble it, and to enroll in the MIACALCIN® Nasal Spray Patient Education Program, please call **1-800-347-BONE**.

Please see your healthcare provider for complete product information for MIACALCIN® Nasal Spray.

CENTER FOR DRUG EVALUATION AND RESEARCH

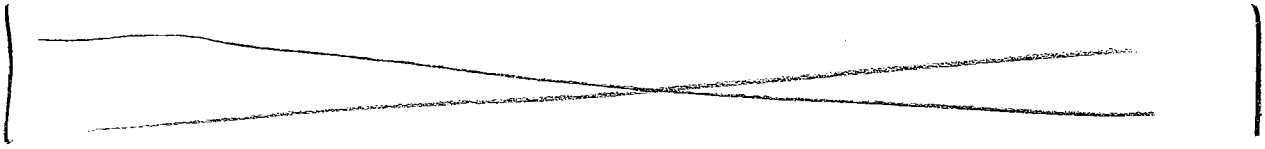
APPLICATION NUMBER:

NDA 20-313/S-023

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1.ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	**20-313**

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER,DATE
Novartis Pharmaceutical Corporation 59 Route 10 East Hanover, NJ 07936-1080 (973) 781-2735	SCS-023, 4/21/03 User Fee date 8/23/03 PA
5. NAME OF THE DRUG 6. NONPROPRIETARY NAME	
Miacalcin Nasal Spray Calcitonin, salmon	
	8. AMENDMENTS/REPORT,DATE
7. SUPPLEMENT PROVIDES FOR:	
A new 30 dose presentation of the drug product.	NA
9. PHARMACOLOGICAL CATEGORY 10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Bone/Calcium-Phosphorous Metabolism Rx	NA
12. DOSAGE FORM 13. POTENCY	
Nasal spray 2200 I.U./mL	
14. CHEMICAL NAME AND STRUCTURE.	



15. COMMENTS

This prior approval Supplement provides for a new presentation of the drug product consisting of a larger 7 mL vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses. Minor changes to analytical testing are made necessitated by the larger product volume. No other changes are made. Supporting data is adequate for the proposed new presentation. Draft labeling to support this change is adequate. For specific chemistry information, see Review Notes.

16. CONCLUSION AND RECOMMENDATION

The supplement is approvable from a chemistry viewpoint. Issue **Approval** (AP) letter.

17. REVIEWER NAME	18. REVIEWER SIGNATURE	19. DATE COMPLETED
Martin Haber, Ph.D.		August 18, 2003

DISTRIBUTION: ORIGINAL JACKET R. Hedin M. Haber DIVISION FILE

R/D Init by: Dr. S. Markofsky acting for Dr. M. Gautam-Basak, Chemistry Team Leader

13 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-313
5023

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Haber
8/19/03 10:24:29 AM
CHEMIST

recommends approval

Sheldon Markofsky
8/19/03 10:37:22 AM
CHEMIST
Signed by S. B. Markofsky, acting Team Leader for
Mamta Gautam-Basak

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-313/S-023

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 20-313/S-023

Name of Drug: Miacalcin (calcitonin-salmon) Nasal Spray

Sponsor: Novartis Pharmaceuticals Corporation

Material Reviewed

Submission Dates:

- April 21, 2003 submission containing draft labeling for the vial label, vial carton, draft package insert, and patient assembly instructions - patient package insert.

Background and Summary Description:

This prior approval supplemental new drug application was submitted on April 21, 2003, and provides for a larger 7 mL vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses, and minor changes to analytical testing.

Review

Package insert

The submitted April 21, 2003, draft text for the PI (Identifier Number 89014604, Issued Date April 2003), was compared to the FPL PI text (Identifier Number 30367903, Issued Date August 1996) submitted October 1, 1996. The following discrepancies are noted:

- The company name is changed from Sandoz to Novartis.

- The sentence, "**CAUTION:** Federal law prohibits dispensing without prescription" is changed to, "**Rx only**." This is in response to the February 1, 2002 Federal Register notice. See Guidance for Industry, Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements. This is an acceptable change.

- In the **DESCRIPTION** section the phrase, "Each milliliter contains" is

deleted, and the amount of sodium chloride, and benzalkonium chloride in the drug product is deleted. Also the phrases *"Active Ingredient:* and *Inactive Ingredients"* are added, and the active ingredient, and inactive ingredients are put into separate sentences.

- [redacted]

- In the **Information for Patients** section the bullet that reads, "After a new bottle is assembled, it should be stored at room temperature in an upright position. Each bottle contains 14 doses." now reads, "Store bottle in use at room temperature between 5°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses. The bullet, "Discard all unrefrigerated bottles after 30 days" has been deleted.

- In the **Miacalcin (calcitonin-salmon) Nasal Spray** subsection of the **HOW SUPPLIED** section the term clear is added after dose, and 3.7 mL replaces 2 ml. Also, the plurality of the paragraph has changed from plural to singular.

- In the *Store and Dispense* subsection of the **HOW SUPPLIED** section the sentences, "Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses." have been deleted, and replaced with, "Store unopened bottle in refrigerator 2°C-8°C (36°F-46°F). Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

- In the **HOW SUPPLIED** section the name, "Sandoz Pharmaceuticals Corporation East Hanover, New Jersey 07936" has been replaced with, "Manufactured by: Novartis Pharma S.A. Huningue, France Distributed by: Novartis Pharmaceuticals Corp. East Hanover, New Jersey 07936."

Vial label

The submitted April 21, 2003, draft text for the vial label (Identifier Number 85059401, No Issued Date), was compared to the FPL vial label text (Identifier Number 22267702, No Issued Date) submitted September 12, 1995. The following discrepancies are noted:

- The company name has changed from "Manufactured for: SANDOZ Pharmaceuticals Corp. East Hanover, NJ 07936" to Manufactured by: Novartis Pharma S.A. Huningue, France © Novartis."

- The NDC number has changed from 0078-0149-75 to 0078-0311-54.

- The sentence, "Store in refrigerator until opened, then at room temperature." now reads, "Store in refrigerator until opened, then at room

temperature in an upright position."

- The phrase, "200 I.U./dose 2200 I.U./mL 2 mL size" now reads, "30 dose bottle 3.7 mL 200 I.U. per actuation."

- The phrase, "CAUTION: Federal law prohibits dispensing without prescription" now reads, "Rx only." This change was made in response to the Guidance for Industry Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements.

Vial carton

The submitted April 21, 2003, draft text for the vial carton (Identifier Number 83037501, No Issued Date), was compared to the FPL vial carton text (Identifier Number 10267701, No Issued Date) submitted October 1, 1996. The following discrepancies are noted:

- The company name has changed from "Manufactured by: SANDOZ Pharma Ltd. Basle, Switzerland, for Sandoz Pharmaceuticals Corporation East Hanover, NJ 07936" to Manufactured by: Novartis Pharma S.A. Huningue, France Distributed by Novartis Pharmaceuticals Corp. East Hanover, NJ 07936."

- The NDC number has changed from 0078-0149-75 to 0078-0311-54.

- The sentence, "Store in refrigerator at 36° to 46°F (2° to 8°) until opened, then at room temperature (for up to 30 days) in an upright position." now reads, "Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) for up to 35 days in an upright position. Store unopened bottle in refrigerator between 2°C-8°C (36°F-46°F) until ready for use."

- The phrase, "200 I.U. calcitonin-salmon per actuation, 2200 I.U./mL" now reads, "30 dose bottle 200 I.U. calcitonin-salmon per actuation."

- The phrase, "CAUTION: Federal law prohibits dispensing without prescription" now reads, "Rx only." This change was made in response to the Guidance for Industry Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements.

- The phrase "200 IU/dose 2mL size," now reads, "3.7 mL bottle & applicator."

- The phrase, Each mL contains: 2200 IU calcitonin salmon *Inactive*

ingredients: benzalkonium chloride, NF hydrochloric acid 25% (w/w), qs to pH 3.7 ± 0.1 sodium chloride, USP purified water, USP nitrogen, NF," now reads, "*Active Ingredient:*calcitonin-salmon, 2200 I.U. per mL (corresponding to 200 I.U. per 0.09 mL actuation). *Inactive Ingredients:* sodium chloride, benzalkonium chloride, hydrochloric acid (added as necessary to adjust pH) and purified water."

- The phrase, "Each container will deliver 14 doses," now reads, "Bottle contains at least 30 doses."

Patient assembly instructions - patient package insert

- The sentence, "There are at least 14 "doses" of MIACALCIN Nasal Spray in each bottle." now reads, " There are at least 30 "doses" of MIACALCIN Nasal Spray in each bottle."

- The following two sentences are added after the above sentence, "You should keep track of the number of doses used from the bottle. After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty."

- The company name has changed from "Novartis Pharmaceuticals Corporation East Hanover, NJ 07936" to Manufactured by: Novartis Pharma S.A. Huningue, France Distributed by Novartis Pharmaceuticals Corp. East Hanover, NJ 07936."

- The format of the HOW TO ASSEMBLE AND USE directions is changed.

Conclusions

The changes to the label are acceptable.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Randy Hedin
8/22/03 09:56:20 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-313/S-023

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attn: Joan A. Materna
Senior Associate Director, Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Materna:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Miacalcin® (salmon calcitonin, synthetic) Nasal Spray
NDA Number:	20-313
Supplement number:	S-023
Date of supplement:	April 21, 2003
Date of receipt:	April 23, 2003

This supplemental application proposes a larger vial of Miacalcin Nasal Spray that delivers 30 doses instead of the currently approved 14 doses.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 22, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 23, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Randy Hedin
5/3/03 10:34:50 AM