

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



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

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=441) 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 with Miacalcin® (calcitonin-salmon)

Adverse Reaction	Miacalcin® (calcitonin-salmon) Nasal Spray N=441 % of Patients	Placebo Nasal Spray N=131 % of Patients
Rhinitis	12.0	6.9
Symptom of Nasel†	10.6	15.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	

†Symptom of nose including nasal pain, dryness, tenderness or erythema, nasal mucus, rhinorrhea, itching, irritation, inflammation, infection, sinusitis, numbness, sneezing, 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 and Fluids - General Disorders: influenza-like symptoms*, fatigue*, periorbital edema*, fever
Immunoreactivity: epiphrenic rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating
Musculoskeletal/Connective Tissue: arthralgia*, arthritis, polymyalgia rheumatica, stiffness
Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, rhinorrhoea*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, anosmia
Cardiovascular/Hypertension: angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction
Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, halitosis, increased appetite, gastritis, dry mouth
Neurological/Psychiatric: dizziness*, vertigo, weight increase
Endocrine/Metabolic: hypothyroidism
Urinary System: cystitis*, gonorrhoea, prostatitis, 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 floaters
Vascular: flushing, cerebrovascular accident, thrombophlebitis
Hematologic/Rheumatism: 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 13% of patients treated with the nasal spray (and 15% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in 25% of patients who take injectable calcitonin-salmon, occurs less frequently in patients treated with injectable calcitonin-salmon. Although the nasal spray is administered with injectable calcitonin-salmon, side effects are comparable. Side effects of injectable and nasal spray calcitonin-salmon are listed in the following table. The incidence of side effects is given as a percentage of patients. The nasal dosage form has a mean bioavailability of about 3% (range 0.3%-50.5%) 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 IU, doses up to 800 IU per day for three days and chronic administration of doses up to 800 IU per day have been studied without serious adverse effects. A dose of 1600 IU administered as a solution given subcutaneously every 2 days for 10 days produced a dose of Miacalcin equivalent to 32 IU 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 parental administration of calcium should be available for the treatment of overdose.

DOSSAGE AND ADMINISTRATION

The recommended dose of Miacalcin® (calcitonin-salmon) Nasal Spray in postmenopausal osteoporotic females is one spray (200 IU) per day administered intranasally, alternating nostrils 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 is available in a 3.7 mL (60 clear glass bottles, 1 is available in a dosage strength of 200 IU per actuation (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 IU 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 bottles in refrigerator between 2°C-8°C (36°F-46°F). Protect from freezing. Store bottles 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.
Hullingue, 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.,
 Hombourg, France

Distributed by:
 Novartis Pharmaceutical Corp.,
 East Hanover, NJ 07926



NOVARTIS NDC 0078-0311-54
 3.7 mL bottle & applicator

Miacalcin
 NASAL SPRAY
 (calcitonin-salmon) Nasal Solution

30 dose bottle
 200 I.U. calcitonin-salmon per actuation
 FOR INTRANASAL USE ONLY
 REFRIGERATE UNTIL OPENED

Rx only
 3.7 mL bottle

NOVARTIS
Miacalcin
 NASAL SPRAY
 (calcitonin-salmon) Nasal Solution

200 I.U. per actuation
 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 16°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.

NOVARTIS NDC 0078-0311-54
 3.7 mL bottle & applicator

Miacalcin
 NASAL SPRAY
 (calcitonin-salmon) Nasal Solution

30 dose bottle
 200 I.U. calcitonin-salmon per actuation
 FOR INTRANASAL USE ONLY
 REFRIGERATE UNTIL OPENED

Rx only
 3.7 mL bottle

NOVARTIS
Miacalcin
 NASAL SPRAY
 (calcitonin-salmon) Nasal Solution
 200 I.U. per actuation
 30 dose bottle
 3.7 mL bottle & applicator





NDC 0078-0511-04

Miacalcin[®]
N A S A L S P R A Y

(calcitonin-salmon) Nasal Solution

30 dose bottle 3.7 mL

200 IU, per actuation **Rx only**

FOR INTRNASAL USE ONLY

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

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

U.S. PATENT NO. 5,367,722

85050401

Information for the Patient

T2003-12
89019501

Miacalcin® (calcitonin-salmon) Nasal Spray

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

MIAACALCIN® 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 MIAACALCIN® 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 MIAACALCIN® 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 MIAACALCIN® Nasal Spray, to treat your condition.

How does MIAACALCIN® Nasal Spray work?

The active ingredient in MIAACALCIN® 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-class], 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 MIAACALCIN® 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 MIAACALCIN® Nasal Spray?

The recommended dose of MIAACALCIN® 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 MIAACALCIN® 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 MIAACALCIN® Nasal Spray?

MIAACALCIN® 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 MIAACALCIN® (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 MIAACALCIN® 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 MIAACALCIN® 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 MIAACALCIN® Nasal Spray. In some cases, your doctor may decide to temporarily discontinue treatment with MIAACALCIN® 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 MIAACALCIN® Nasal Spray.
- MIAACALCIN® 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 MIAACALCIN® Nasal Spray very well; however, like all prescription drugs, MIAACALCIN® 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 MIAACALCIN® 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 MIAACALCIN® Nasal Spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to assemble, prime, and use MIAACALCIN® Nasal Spray. In addition, detailed directions can be found in your MIAACALCIN® 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 MIAACALCIN® Nasal Spray and all medicines out of reach of children. This leaflet provides a summary of information about MIAACALCIN® Nasal Spray. If you have any questions or concerns about either MIAACALCIN® Nasal Spray or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other healthcare provider.



10561068

Novartis Pharmaceuticals Corporation
Y A R P S T V S N
Miacalcin

Miacalcin®
N A S A L S P R A Y



(calcitonin-salmon) Nasal Solution



89019501

NOVARTIS

Manufactured by:
Novartis Pharma S.A.S.
Huntingue, 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.

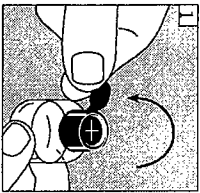
Important Facts About Your Medication:

- 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.

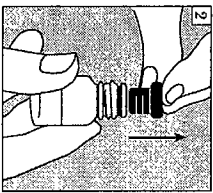
HOW TO USE MIACALCIN® (calcitonin-salmon) NASAL SPRAY

Putting the Nasal Spray Pump Unit Together

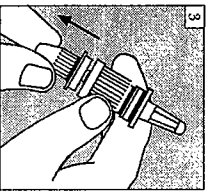
1. If your bottle and pump unit were already assembled by your pharmacist, go to step 6. If not, remove the bottle from your refrigerator and allow it to reach room temperature before assembling. Lift up the blue plastic tab and carefully pull the metal safety seal off the bottle.



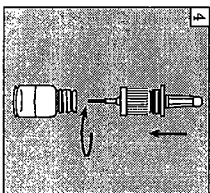
2. Keeping the bottle upright, remove the rubber stopper from the bottle.



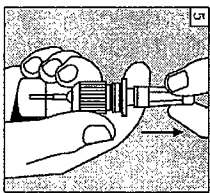
3. Holding the pump unit, gently remove the opaque plastic protective cap from the bottom of the unit.
Note: Do not depress pump when it is not attached to the bottle.



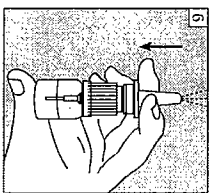
©Novartis



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.



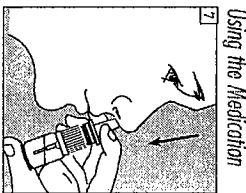
5. Holding the bottle upright with your index finger on top of one of the two side arms of the pump, gently remove the clear protective cap from the top of the nozzle.



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.

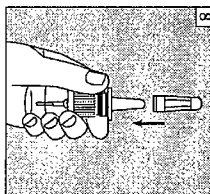


Using the Medication

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.



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
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	User Fee date 8/23/03 PA
Miacalcin Nasal Spray	Calcitonin, salmon	
7. SUPPLEMENT PROVIDES FOR:		8. AMENDMENTS/REPORT, DATE
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		
<p>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.</p>		
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

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/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.

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- 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

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/s/

Randy Hedin
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CSO

