CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076396

Name: Calcitonin-Salmon Nasal Spray
200 IU/Spray

Sponsor: Apotex Corp.

Approval Date: November 17, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-396

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kiran Krishnan
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 8, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Calcitonin-Salmon Nasal Spray, 200 IU/Spray, packaged in 2 mL and 3.7 mL fill volumes.

Reference is also made to your amendments dated April 23, 2003; June 10, July 29 (2 submissions), and August 13, 2004; January 31, April 19, May 18, August 18, August 30, and September 1, 2005; February 23, and April 5, 2006; February 20, July 23, November 9, and November 28, 2007; and April 30, July 18, and July 22, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Calcitonin-Salmon Nasal Spray, 200 IU/Spray, packaged in 2 mL and 3.7 mL fill volumes to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Miacalcin Nasal Spray of Novartis Pharmaceuticals Corporation.

The RLD upon which you have based your ANDA, Miacalcin Nasal Spray, 200 IU/spray of Novartis Pharmaceuticals Corporation (Norvartis), is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"),

U.S. Patent Nos. 5,733,569 (the '569 patent) and 5,759,565 (the '565 patent) are scheduled to expire on March 31, 2015.

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Calcitonin-Salmon Nasal Spray, 200 IU/Spray, packaged in 2 mL and 3.7 mL fill volumes, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Apotex Inc. (Apotex) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must have been brought against Apotex prior to the expiration of 45 days from the date the notice you provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Apotex complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Apotex for infringement of the '569 and '565 patents in the United States District Court for the Southern District of New York [Novartis Pharmaceuticals Corp. v. Apotex Corp., Civil Action No. 02 CV 8917]. Although this litigation remains ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, has expired.

With respect to 180-day generic drug exclusivity, we note that Apotex was the first ANDA applicant to submit a substantially complete ANDA with paragraph IV certifications to the '569 and '565 patents. Therefore, with this approval, Apotex is eligible for 180-days of generic drug exclusivity for Calcitonin-Salmon Nasal Spray, 200 IU/Spray packaged in 2 mL and 3.7 mL fill volumes. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv).[1] Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

---

[1]Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence - SPL for Approved ANDA"***.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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/

Gary Buehler
11/17/2008 04:36:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

LABELING

14" (355.6 mm)

7" (177.8 mm)

For position only

0.984" (25 mm)

204608

PRESCRIBING INFORMATION

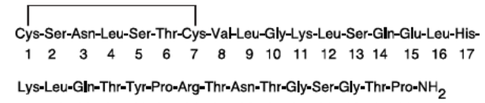
℞ Only

Calcitonin-Salmon Nasal Spray

DESCRIPTION

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

Calcitonin-salmon nasal spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in 2 mL fill glass bottles as a solution for nasal administration. This is sufficient medication for at least 14 doses.

Active Ingredient: calcitonin-salmon, 2200 IU per mL (corresponding to 200 IU per 0.09 mL spray).

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

Calcitonin-salmon nasal spray, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis - In two clinical studies designed to evaluate the pharmacodynamic response to calcitonin-salmon nasal spray, administration of 100-1600 IU 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 IU did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney - Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with calcitonin-salmon nasal spray.

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

Pharmacokinetics and Metabolism

The data on bioavailability of calcitonin-salmon nasal spray obtained by various investigators using different methods show great variability. Calcitonin-salmon 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 - Calcitonin-salmon nasal spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Calcitonin-salmon nasal spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of calcitonin-salmon nasal spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 IU per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females [227 calcitonin-salmon nasal spray treated and 98 placebo treated] with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 IU daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Calcitonin-salmon nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as six months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 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 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 calcitonin-salmon injection. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Customer Service department of Apotex Corp. (1-800-4-APOTEX).

PRECAUTIONS

1. Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with calcitonin-salmon nasal spray ingredients.

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 calcitonin-salmon nasal spray.

2. Periodic Nasal Examinations

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

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

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

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

3. Information for Patients

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

Patients should be advised of the following:

- Store new, unopened bottles in the refrigerator between 2°-8°C (36°-46°F).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.

PATIENT'S INSTRUCTIONS FOR USE

Calcitonin-Salmon Nasal Spray

One Spray, Once a Day

BEFORE USING CALCITONIN-SALMON NASAL SPRAY

This package contains two bottles of calcitonin-salmon nasal spray. You should open and use only one bottle at a time. Leave the other bottle in the refrigerator until you are ready to use it.

Important Facts About Your Medication:

- The bottles contain he p oper amount of medication - be aware that he entire bottle will not be filled wi h liquid
- Before opening your medication bottles, keep them in your refrigerator at 2°-8°C (36°- 46°F). Do not freeze
- After opening a new medication bottle, keep it at oom temperature, 20°-25°C (68°-77°F) in an upright position

HOW TO USE CALCITONIN-SALMON NASAL SPRAY

Figure 1

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

Priming a New Bottle

2. To ensure p oper delivery of medication, a newly opened bottle must be primed before you use it for he first time. Holding he bottle upright wi h your index and middle fingers on he two shoulder areas of he pump, and your humb on he bottom of he bottle, press he shoulders down fully **until you see a full spray** (Figure 2). Now he nasal spray is ready for use.

Figure 2

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

Using the Medication

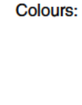


Figure 3

3. The recommended dose of calcitonin-salmon nasal spray is one spray once a day in one nostril. Keep your head upright and carefully place he nozzle in one nostril.

   Tilt he bottle until it is in a straight line wi h the nasal passage (Figure 3).

   Firmly press down on the pump once to spray he medication into your nose. It is not necessary to inhale while his 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 ei her case, he medication is absorbed. IMPORTANT: Do not "test" he spray unit or prime it before you use your daily dose because this will waste your medication.

Cleaning the Pump

4. Once or twice a week, wipe he nozzle wi h a clean, damp clo h. Dry he nozzle before replacing he dust cap.

Storing the Unit

5. Replace he blue safety clip, hen replace he p otective cap on he nasal spray unit (Figure 4). **Be careful not to depress the pump** while his is being done. Once he pump is primed, he unit must be kept at oom temperature (20°-25°C [68°-77°F]) in he upright position until the medication is finished.

Figure 4

IMPORTANT

- Do not refrigerate he unit between doses.
- In the unlikely event hat more han one bottle is opened at one time, please keep he bottle(s) hat are not in use in he refrigerator.
- Do not store the unit on its side.

Bottles left at oom temperature (opened or unopened) for more han 30 days must be discarded.

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

Alternate Nostrils Daily

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

It is important to receive he correct daily amount of calcium and vitamin D, as directed by your heal hcare p ovider.

IMPORTANT

- Use calcitonin-salmon nasal spray daily. To ensure p oper treatment, it is important to use your calcitonin-salmon nasal spray daily even if you have no symptoms of postmenopausal osteopo osis.

What is the Correct Dose of Calcitonin-Salmon Nasal Spray?

A single spray of 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 calcitonin-salmon nasal spray contains at least 14 doses. Priming he pump as described in step 2 does not alter the total number of doses available in a bottle of calcitonin-salmon nasal spray. The bottle need only be primed once. Do not reprime or "test spray" your bottle before you use your daily dose of calcitonin-salmon nasal spray. This will waste your medication.

Please see your heal hcare p ovider for complete p oduct information for calcitonin-salmon nasal spray.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

204608

February 2006

Perforation

Calcitonin-Salmon Nasal Spray
SAP 204608, RA Rev. 4 - Date Revised: 02/21/06 Text Amends.
Flat Size: 14" x 7" - Finished Folded Size 7" x 0.984"
Colours: Black

14" (355.6 mm)

7" (177.8 mm)

0.984" (25 mm)

Information for the Patient
Calcitonin-Salmon Nasal Spray
One Spray, Once A Day

What is calcitonin-salmon nasal spray?
Calcitonin-salmon nasal spray is a medication used for the treatment of osteoporosis after menopause (postmenopausal osteoporosis) in women more than 5 years after menopause wi h low bone mass who refuse or cannot tolerate estrogens, or in whom estrogens are not an option.

Patients who use calcitonin-salmon nasal spray should be su e to ingest adequate amounts of calcium and vitamin D along w th therapy.

How much calcium and vitamin D do I need each day?
When taking calcitonin-salmon nasal spray, it is recommended that you get at least 1000 mg of calcium and 400 IU (inte national units) of vitamin D each day. Check w th your doctor or hea thcare provider to see if you a e getting enough calcium and vitamin D in your diet. If not, he or she may ecommend hat you start taking calcium and vitamin D supplements.

What is osteoporosis after menopause? What causes it?
Postmenopausal osteoporosis is a condition associated wi h 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 dec ease in the amount of estrogen produced. Estrogen in your body helps keep bones strong - w thout it, hey may become weak.

Postmenopausal osteoporosis begins wi hout 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 hea thcare provider can p escribe a medication, like calcitonin-salmon nasal spray, to treat your condition.

How does calcitonin-salmon nasal spray work?
The active ingredient in calcitonin-salmon nasal spray is calcitonin, a man-made protein similar to one found in people, other mammals, and some types of fish and bi ds.

The way calcitonin affects bone is still being studied, but it is believed to work in he following ways:
- Calcitonin educes he activity of osteoclasts [AHS-tee-oh-clasts], the cells hat remove "old" bone
- Because bone building continues while bone removal is slowed down, he result is an inc ease in bone mass

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

How do I use calcitonin-salmon nasal spray?
The recommended dose of calcitonin-salmon nasal spray is one spray daily in alte nated nostrils- unless directed otherwise by your heal hcare provider. Start wi h a spray in the left nostril on your first day, followed by a spray in he right nostril on he second day. Continue to alte nate nostrils every day. The e are at least 14 "doses" of calcitonin-salmon nasal spray in each bottle. You should keep track of he number of doses used from he bottle. **After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**

Who should not take calcitonin-salmon nasal spray?
Calcitonin-salmon nasal spray should not be used by patients who are allergic to he protein calcitonin-salmon, or by women who are pregnant or nursing.

You should be aware of these warnings and precautions when taking calcitonin-salmon nasal spray.
- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed wi h he use of calcitonin-salmon nasal spray. You should inform your doctor and pharmacist about he o her prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking calcitonin-salmon nasal spray. For this reason, it is recommended that a nasal examination be performed prior to he start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with calcitonin-salmon nasal spray. In some cases, your doctor may decide to temporarily discontinue treatment w th calcitonin-salmon nasal spray until symptoms subside.
- Because calcitonin-salmon is a protein, he possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use calcitonin-salmon nasal spray.
- Calcitonin-salmon nasal spray is safe to use in elderly patients. 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 t eatment with calcitonin-salmon nasal spray very well; however, like all prescription drugs, calcitonin-salmon nasal spray may cause some side effects in some people. These side effects are usually mild and generally do not lead to discontinuation of treatment w th calcitonin-salmon nasal spray. The most commonly reported side effects a e:
- Nasal symptoms such as runny nose, crusting or nasal bleeding
- Back/joint pain
- Headache

Anytime you have a medical problem you think may be related to calcitonin-salmon nasal spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to prime and use calcitonin-salmon nasal spray. In addition, detailed directions can be found in your calcitonin-salmon nasal spray box. Please read them carefully before using the spray.

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

- Store bottle in use at room temperature in an upright position, for up to 30 days. Each bottle contains at least 14 doses.
- Store second bottle in refrigerator until ready to use. Protect from freezing.
- Discard all unrefrigerated bottles after 30 days.
- See **DOSAGE AND ADMINISTRATION**, Priming (Activation) of Pump for complete instructions on priming the pump and administering calcitonin-salmon nasal spray. You should keep track of the number of doses used from the bottle. **After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**

4. 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 IU 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*.

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

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

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

7. 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.

8. Pediatric Use
There are no data to support the use of calcitonin-salmon nasal spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

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

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

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

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

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

OVERDOSAGE
No instances of overdose with calcitonin-salmon nasal spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of calcitonin-salmon nasal spray up to 1600 IU, doses up to 800 IU per day for three days and chronic administration of doses up to 600 IU per day have been studied without serious adverse effects. A dose of 1000 IU of calcitonin-salmon injectable solution given subcutaneously may produce nausea and vomiting. A dose of calcitonin-salmon injectable solution of 32 IU per kg per day for one or two days demonstrated no additional adverse effects.

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

DOSAGE AND ADMINISTRATION
The recommended dose of calcitonin-salmon nasal spray in postmenopausal osteoporotic females is one spray (200 IU) per day administered intranasally, alternating nostrils daily.

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

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

HOW SUPPLIED
Calcitonin-Salmon Nasal Spray is available as a metered dose solution in 2 mL fill glass bottles. It is available in a dosage strength of 200 IU per activation (0.09 mL/spray). The pumps, following priming, will deliver 0.09 mL of solution. Calcitonin-Salmon Nasal Spray contains 2200 IU/mL calcitonin-salmon and is provided in individual boxes containing two glass bottles with attached pumps (NDC 60505-0823-0).

Store and Dispense
Store unopened bottle(s) in refrigerator between 2°-8°C (36°-46°F). Protect from freezing. Store bottle in use at room temperature 20°-25°C (68°-77°F) in an upright position, for up to 30 days. Each bottle contains at least 14 doses.

Store second bottle in refrigerator until ready to use. Protect from freezing.

Discard all unrefrigerated bottles after 30 days.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

204608

February 2006

Perforation

For Position Only

14" (355.6 mm)

7" (177.8 mm)

0.984" (25 mm)

FOR POSITION ONLY

PRESCRIBING INFORMATION

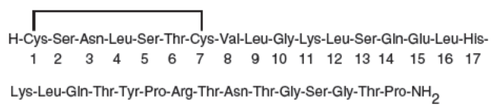
℞ Only

Calcitonin-Salmon Nasal Spray

DESCRIPTION

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

Calcitonin-salmon nasal spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in 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 IU per mL (corresponding to 200 IU per 0.09 mL spray).

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

Calcitonin-salmon nasal spray, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis - In two clinical studies designed to evaluate the pharmacodynamic response to calcitonin-salmon nasal spray, administration of 100-1600 IU 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 IU did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney - Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with calcitonin-salmon nasal spray.

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

Pharmacokinetics and Metabolism

The data on bioavailability of calcitonin-salmon nasal spray obtained by various investigators using different methods show great variability. Calcitonin-salmon 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 - Calcitonin-salmon nasal spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Calcitonin-salmon nasal spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of calcitonin-salmon nasal spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 IU per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females [227 calcitonin-salmon nasal spray treated and 98 placebo treated] with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 IU daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Calcitonin-salmon nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as six months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 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 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 calcitonin-salmon injection. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Customer Service department of Apotex Corp. (1-800-4-APOTEX).

PRECAUTIONS

1. Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with calcitonin-salmon nasal spray ingredients.

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 calcitonin-salmon nasal spray.

2. Periodic Nasal Examinations

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

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

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

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

3. Information for Patients

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

Patients should be advised of the following:

- Store new, unopened bottles in the refrigerator between 2°-8°C (36°-46°F).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.

PATIENT'S INSTRUCTIONS FOR USE

℞ Only

Calcitonin-Salmon Nasal Spray

One Spray, Once a Day

BEFORE USING CALCITONIN-SALMON NASAL SPRAY

This package contains one bottle of calcitonin-salmon nasal spray with attached 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 your medication bottles, keep it in your refrigerator at 2°-8°C (36°- 46°F). Do not freeze
- After opening a new medication bottle, keep it at room temperature, 20°-25°C (68°-77°F) in an upright position

HOW TO USE CALCITONIN-SALMON NASAL SPRAY

Figure 1

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

Priming a New Bottle

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

Figure 2

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

Using the Medication

Figure 3

3. The recommended dose of calcitonin-salmon nasal spray is one spray once a day in one nostril. Keep your head upright and carefully place the nozzle in one nostril.

   Tilt the bottle until it is in a straight line with the nasal passage (Figure 3).

   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

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

Storing the Unit

5. Replace the blue safety clip, then replace the protective cap on the nasal spray unit (Figure 4). **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 20°- 25°C (68°- 77°F) in the upright position until the medication is finished.

Figure 4

IMPORTANT

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

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

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

Alternate Nostrils Daily

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

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

IMPORTANT

- Use calcitonin-salmon nasal spray daily. To ensure proper treatment, it is important to use your calcitonin-salmon nasal spray daily even if you have no symptoms of postmenopausal osteoporosis.

What is the Correct Dose of Calcitonin-Salmon Nasal Spray?

A single spray of 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 calcitonin-salmon nasal spray contains at least 30 doses. Priming the pump as described in step 2 does not alter the total number of doses available in a bottle of calcitonin-salmon nasal spray. The bottle need only be primed once. Do not reprime or "test spray" your bottle before you use your daily dose of calcitonin-salmon nasal spray. This will waste your medication.

Please see your healthcare provider for complete product information for calcitonin-salmon nasal spray.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

TBD

February 2006

Perforation →

Calcitonin-Salmon Nasal Spray 3.7 mL
SAP Code: TBD, RA Rev. 0 - **Date Created:** 02/22/06
Flat Size: 14" x 7" - **Finished Folded Size:** 7" x 0.984" -
Colours: Black

14" (355.6 mm)

7" (177.8 mm)

0.984" (25 mm)

Information for the Patient
Calcitonin-Salmon Nasal Spray

What is calcitonin-salmon nasal spray?
Calcitonin-salmon nasal spray is a medication used for the treatment of osteoporosis after menopause (postmenopausal osteoporosis) in women more than 5 years after menopause wi h low bone mass who refuse or cannot tolerate estrogens, or in whom estrogens are not an option.

Patients who use calcitonin-salmon nasal spray should be su e to ingest adequate amounts of calcium and vitamin D along w th therapy.

How much calcium and vitamin D do I need each day?
When taking calcitonin-salmon nasal spray, it is recommended that you get at least 1000 mg of calcium and 400 IU (inte national units) of vitamin D each day. Check w th your doctor or hea thcare provider to see if you a e getting enough calcium and vitamin D in your diet. If not, he or she may ecommend hat you start taking calcium and vitamin D supplements.

What is osteoporosis after menopause? What causes it?
Postmenopausal osteoporosis is a condition associated wi h 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 hrough menopause. At menopause, a woman's body goes through many changes, including a substantial dec ease in the amount of estrogen produced. Estrogen in your body helps keep bones strong - w thout it, hey may become weak.

Postmenopausal osteoporosis begins wi hout 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 hea thcare provider can prescribe a medication, like calcitonin-salmon nasal spray, to treat your condition.

How does calcitonin-salmon nasal spray work?
The active ingredient in calcitonin-salmon nasal spray is calcitonin, a man-made protein similar to one found in people, other mammals, and some types of fish and bi ds.

The way calcitonin affects bone is still being studied, but it is believed to work in he following ways:
- Calcitonin educes he activity of osteoclasts [AHS-tee-oh-clasts], the cells hat remove "old" bone
- Because bone building continues while bone removal is slowed down, he result is an inc ease in bone mass

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

How do I use calcitonin-salmon nasal spray?
The recommended dose of calcitonin-salmon nasal spray is one spray daily in alte nated nostrils- unless directed otherwise by your heal hcare provider. Start wi h a spray in the left nostril on your first day, followed by a spray in he right nostril on he second day. Continue to alte nate nostrils every day. There are at least 30 "doses" of calcitonin-salmon nasal spray in each bottle. You should keep track of he number of doses used from he bottle. **After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**

Who should not take calcitonin-salmon nasal spray?
Calcitonin-salmon nasal spray should not be used by patients who are allergic to he protein calcitonin-salmon, or by women who are pregnant or nursing.

You should be aware of these warnings and precautions when taking calcitonin-salmon nasal spray.
- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed wi h he use of calcitonin-salmon nasal spray. You should inform your doctor and pharmacist about he o her prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking calcitonin-salmon nasal spray. For this reason, it is recommended that a nasal examination be performed prior to he start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with calcitonin-salmon nasal spray. In some cases, your doctor may decide to temporarily discontinue treatment w th calcitonin-salmon nasal spray until symptoms subside.
- Because calcitonin-salmon is a protein, he possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use calcitonin-salmon nasal spray.
- Calcitonin-salmon nasal spray is safe to use in elderly patients. 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 t eatment with calcitonin-salmon nasal spray very well; however, like all prescription drugs, calcitonin-salmon nasal spray may cause some side effects in some people. These side effects are usually mild and generally do not lead to discontinuation of treatment w th calcitonin-salmon nasal spray. The most commonly reported side effects a e:
- Nasal symptoms such as runny nose, crusting or nasal bleeding
- Back/joint pain
- Headache

Anytime you have a medical problem you think may be related to calcitonin-salmon nasal spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to prime and use calcitonin-salmon nasal spray. In addition, detailed directions can be found on the reverse side of this insert. Please read them carefully before using the spray.

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

- Store bottle in use at room temperature 20°- 25°C (68°- 77°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.
- See **DOSAGE AND ADMINISTRATION**, Priming (Activation) of Pump for complete instructions on priming the pump and administering calcitonin-salmon nasal spray. You should keep track of the number of doses used from the bottle. **After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**

4. 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 IU 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*.

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

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

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

7. 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.

8. Pediatric Use
There are no data to support the use of calcitonin-salmon nasal spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

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

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

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

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

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

OVERDOSAGE
No instances of overdose with calcitonin-salmon nasal spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of calcitonin-salmon nasal spray up to 1600 IU, doses up to 800 IU per day for three days and chronic administration of doses up to 600 IU per day have been studied without serious adverse effects. A dose of 1000 IU of calcitonin-salmon injectable solution given subcutaneously may produce nausea and vomiting. A dose of calcitonin-salmon injectable solution of 32 IU per kg per day for one or two days demonstrated no additional adverse effects.

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

DOSAGE AND ADMINISTRATION
The recommended dose of calcitonin-salmon nasal spray in postmenopausal osteoporotic females is one spray (200 IU) per day administered intranasally, alternating nostrils daily.

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

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

HOW SUPPLIED
Calcitonin-Salmon Nasal Spray is 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 IU per spray (0.09 mL/spray). The pump, following priming, will deliver 0.09 mL of solution. Calcitonin-Salmon Nasal Spray contains 2200 IU/mL calcitonin-salmon and is provided in an individual box containing one glass bottle with attached pump (NDC 60505-0823-6).

Store and Dispense
Store unopened bottle in refrigerator between 2°-8°C (36°-46°F). Protect from freezing. Store bottle in use at room temperature 20°-25°C (68°-77°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

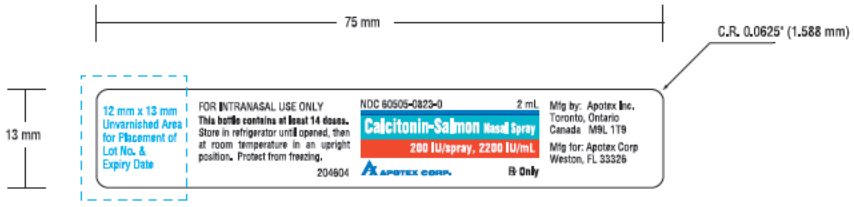
TBD

February 2006

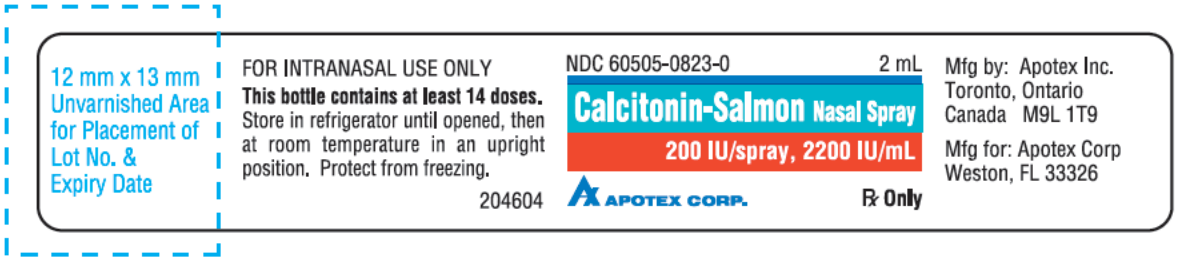
Perforation

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - **Richmond Hill Site** 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIAL PROOF		Copy of	Date May 16, 2005
Material Code 204604	Product Name LBL: CALCITONIN SALMON NASAL SPRAY 200 IU/SPRAY - 2ML		
Previous Code N/A	Label size 75 mm x 13 mm		Change: Update mfg by address and add text to left panel. (rev3) Revised text as per labeling deficiencies dated May 10/2005. (rev4)
Colour (s) Black Blue - (b) (4) Aqua Red - (b) (4)	Web Direction: Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. (PRINTING READS THIS WAY)	Printing (b) (4) / Caliper (b) (4)	Paper Stock (b) (4) / Adhesive Permanent
Prepared by:	Date:		Reg. Affairs Revision No.: 4

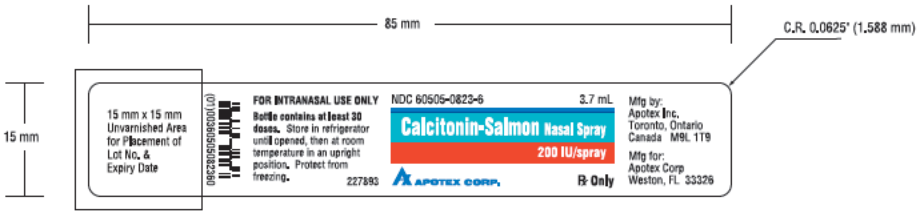


200% Zoom



APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - **Richmond Hill Site** 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIAL PROOF		Copy of	Date May 17, 2005
Material Code 227893	Product Name LBL: USA CALCITONIN N/SPRY 200IU 3.7ML		
Previous Code N/A	Label size 85 mm x 15 mm		Change: Revised text as per labeling deficiencies dated May 10/2005.
Colour (s) Black, Blue - Aqua, Red - (b) (4)	Web Direction: Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. (PRINTING READS THIS WAY)	Printing (b) (4) / Caliper (b) (4)	Paper Stock (b) (4) / Adhesive Permanent	
Prepared by:	Date:		Reg. Affairs Revision No.: 1



200% Zoom

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - Richmond Hill Site 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIAL PROOF			Copy of	Date July 09, 2004
Material Code 207258	Product Name CTN: CALCITONIN SALMON NAS SPR 200 IU 2ML X 2			
Previous Code 204606	Label size Docket #2736E - 4 59 mm x 39 mm x 102 mm			Change: Update mfg address revise storage conditions & add 14 doses per bottle.
Colour (s) Black Blue - Aqua Red - (b) (4) (b) (4)		Printing Offset	Paper Stock N/A	
		Caliper N/A	Adhesive N/A	
Prepared by:		Date:		Reg. Affairs Revision No.: 1

207258

Unvarnished Area
(45 mm x 15 mm)
for placement of Lot No. & Expiry Date

NDC 60505-0823-0 2 x 2 mL bottles

Calcitonin-Salmon
Nasal Spray

200 IU calcitonin-salmon per spray, 2200 IU/mL

FOR INTRANASAL USE ONLY

14 Doses Per Bottle

℞ Only

REFRIGERATE UNTIL OPENED

APOTEX CORP.

USUAL DOSAGE:
One 200 IU spray per day. See Prescribing Information insert for further dosage information. Important patient information enclosed.

Each spray will dispense 0.09 mL, which will contain 200 IU (one dose) of calcitonin-salmon. Each bottle contains at least 14 doses.

FOR INTRANASAL USE ONLY

Store bottle in use at room temperature 20°-25°C (68°-77°F) [for up to 30 days] in an upright position. Store second bottle in refrigerator at 2°-8°C (36°-46°F) until ready to use. Protect from freezing.

NDC 60505-0823-0 2 x 2 mL bottles

Calcitonin-Salmon
Nasal Spray

200 IU calcitonin-salmon per spray, 2200 IU/mL

FOR INTRANASAL USE ONLY

14 Doses Per Bottle

℞ Only

REFRIGERATE UNTIL OPENED

APOTEX CORP.

Active Ingredient:
calcitonin-salmon, 2200 IU per mL (corresponding to 200 IU per 0.09 mL spray).
Inactive Ingredients:
benzalkonium chloride, hydrochloric acid (added as necessary to adjust pH), purified water and sodium chloride.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

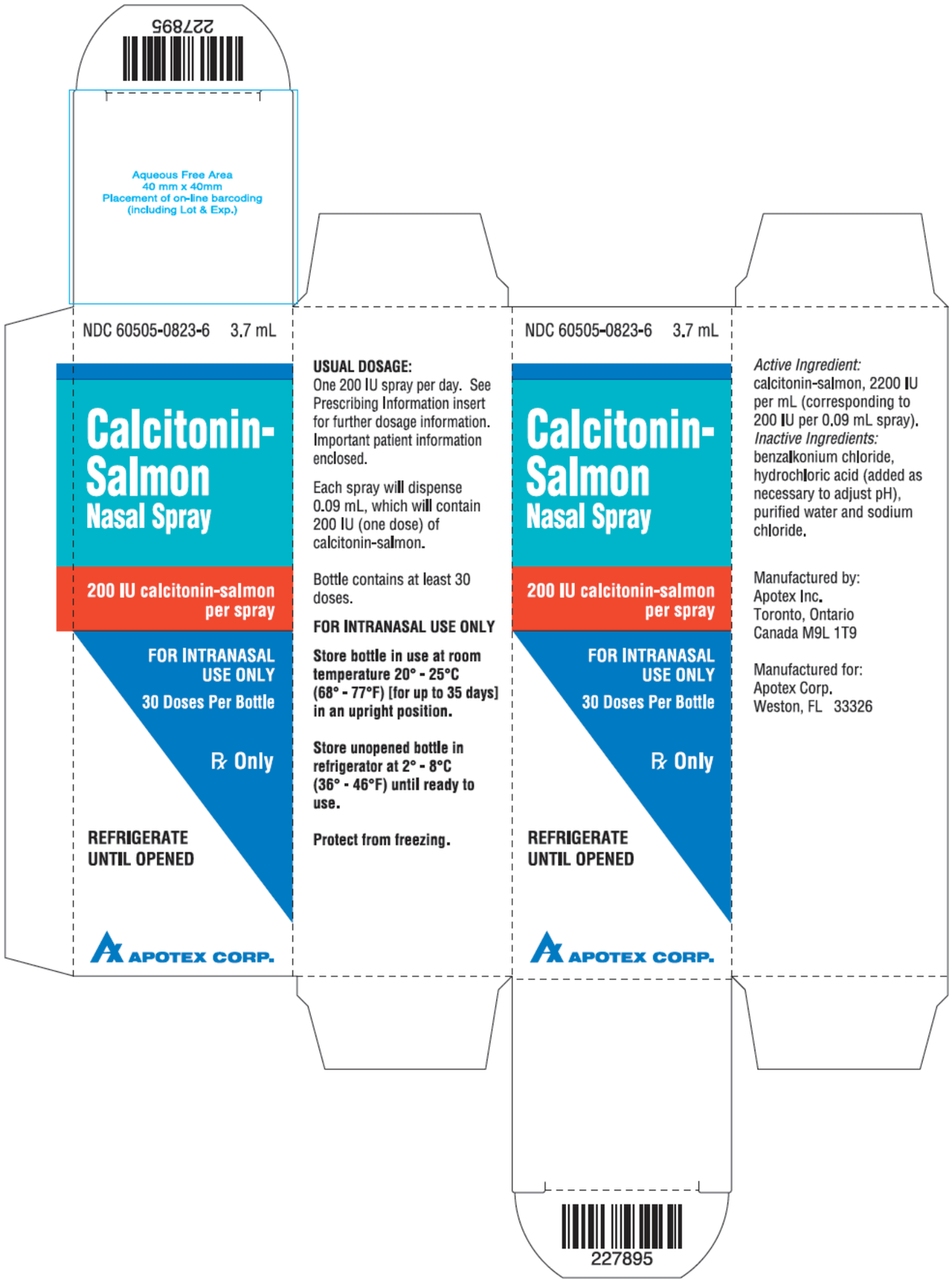
Manufactured for:
Apotex Corp.
Weston, FL 33326

3 60505 08230 8

207258

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - Richmond Hill Site 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIAL PROOF			Copy of	Date May 16, 2005
Material Code 227895	Product Name CTN: USA CALCITONIN N/SPRY 200IU 3.7ML			
Previous Code N/A	Label size 40 mm x 40 mm x 122.5 mm Dwg# 973E0			Change: Revised text as per labeling deficiencies dated May 10/2005.
Colour (s) Black Blue - (b) (4) Aqua Red - (b) (4)		Printing Offset	Paper Stock N/A	
		Caliper N/A	Adhesive N/A	
Prepared by:		Date:		Reg. Affairs Revision No.: 1



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

LABELING REVIEWS

****First Generic****
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-396
Date of Submissions:	July 15, 2002 and April 8, 2002 (Original draft labeling)
Applicant's Name:	Novex Pharma
Established Name:	Calcitonin-Salmon Nasal Spray, 200 IU/spray

---

Labeling Deficiencies:

1. **CONTAINER** (2 mL bottle):

   Assure that the established name and strength appear as the most prominent information.

2. **CARTON** (2 x 2mL bottles):

   a. Revise the inactive ingredients section to reflect the removal of [redacted] (b) (4) from the formulation.

   b. We encourage you to include the product name and strength on the top panel.

3. **INSERT**

   a. DESCRIPTION
   Revise the inactive ingredients section to reflect the removal of [redacted] (b) (4) from the formulation

   b. WARNINGS, Allergic Reactions subsection
   Revise the second paragraph to read:
   [redacted] (b) (4)

4. **PATIENT INSTRUCTIONS**

   a. TITLE
   Add "One Spray, Once a Day" as the third line

   b. What is the Correct Dose of Calcitonin-Salmon Nasal Spray?
   The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. In accordance with 21 CFR 314.94(a)(8)(iii), you are required to offer a similar program. Please comment.

5. INFORMATION FOR THE PATIENT

a. *What is osteoporosis after menopause? What causes it?*
Fourth paragraph, fourth sentence- revise to read "...medication, like calcitonin-salmon nasal spray, to..." [insert comma after "spray"]

b. *How does calcitonin-salmon nasal spray work?*
Second paragraph-revise "osteclasts" to read "osteoclasts"

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition?
- What is the RLD on the 356(h) form:
- NDA Number:
- NDA Drug Name:
- NDA Firm:
- Date of Approval of NDA Insert and supplement #:
- Has this been verified by the MIS system for the NDA?
- Was this approval based upon an OGD labeling guidance?
- Basis of Approval for the Container Labels:
- Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			X
Is the scoring configuration different than the RLD?			X
			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313)

- Package Insert S-003, revised August 1996 and approved March 7, 1997
  However, the WARNINGS section was revised in a November 2002 package found on the company's website. I used the Nov. 2002 version as the RLD for the first paragraph in the WARNINGS section (re: one case of anaphylactic shock).
- Instructions for use "How to assemble and use", S-002, revised May 1996 and approved October 22, 1996. However, I also used the RLD Instructions provided by the ANDA applicant as reference because some of the information has been updated since 1996 to reflect two (instead of one) bottle per carton, cleaning the pump, and some storage considerations.
- Information for the patient, S-010, revised March 1999 and approved in FPL August 28, 2002
- Carton: Side-by-side comparison with innovator labels in jacket.
- Container, S-002 approved October 22, 1996

Note: Novex Pharma Patient's Instructions for Use and Information for the Patient come as a

perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31,2015	U-227
020313	002	5759565	MAR 31,2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.2, pg 566]

4. CONTAINER/CLOSURE

Package Size 2 mL
Bottle: 3 mL (b) (4) clear type I glass
Nasal Spray Pump: 91 μL Nasal Spray Pump with white actuator and cap

[Vol. A1.2, pg. 686]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is NOT consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. In the September 11, 2002 submission, Novex revised the formulation to remove (b) (4) (in order to be Q1/Q2 to the innovator.) The firm also committed to revising the product labeling to reflect the removal of (b) (4).

Note: In NDA 20-313/S-018, Novartis deleted (b) (4).

6. PACKAGING CONFIGURATIONS

RLD: Two 2-mL vials and applicators per carton
ANDA: Two 2-mL bottles per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately). [Chem. Review #1]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: N/A
RLD: Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.

Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36 ° F to 46 ° F (2 ° C to 8 ° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36 ° F to 46 ° F (2 ° C to 8 ° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.

ANDA: Container & Carton-same as rld
Insert- Store bottle in use at room temperature in an upright position for up to 30 days. Each bottle contains at least 14 doses. Store second bottle in refrigerator until ready to use. Protect from freezing. Discard all unrefrigerated bottles after 30 days.

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:

The firm's bioequivalency data is under review by the Division of Bioequivalence as January 3, 2003.

Date of Review: 1/6/03 & 1/23/03

Date of Submission: July 12, 2002 (The 4/8/02 submission was "refused to receive")

Primary Reviewer: Ruby Wu Ruby **Date:** 3/14/03

Team Leader: John Grace John M Grace **Date:** 3/17/2003

cc:
ANDA: 76-396
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\NOVEX\LTRS&REV\76396.NA1.L.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-396
Date of Submissions:	April 23, 2003 and February 25, 2004 (Amendments)
Applicant's Name:	Novex Pharma
Established Name:	Calcitonin-Salmon Nasal Spray, 200 IU/spray

---

Labeling Deficiencies:

1. **CONTAINER** (2 mL bottle):
   If space permits, we encourage you to add "14 Dose Bottle".

2. **CARTON** (2 x 2mL bottles):
   a. Main Panels-We encourage you to add "14 Doses Per Bottle".
   b. Side panel- "Store bottle in use at room temperature 20°-25°C (68°-77°F) [for up to 30 days]...second bottle in refrigerator at 2°-8°C (36°-46°F) until..."

3. **INSERT**
   a. WARNINGS, Allergic Reactions subsection
      Revise the second paragraph to read:
      "For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of calcitonin-salmon injection. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the XXXX Department of Novex Pharma." Please revise the last sentence accordingly. A copy of the skin testing protocol is attached. Please submit, for our review and comment, a similar skin testing protocol that will be provided to practitioners who may request a copy of the protocol. Assure that the protocol will be available when your ANDA is approved.
   b. PRECAUTIONS, Information for Patients, Seventh bullet: add as the last 2 sentence: "You should keep track of the number of doses used from the bottle. **After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**"
   c. HOW SUPPLIED, Store and Dispense: "Store unopened bottle(s) in refrigerator between 2°-8°C (36°-46°F)...Stgore bottle in use at room temperature 20°-25°C (68°-77°F) in an..."

4. **PATIENT INSTRUCTIONS**
   a. Important Facts About Your Medication
      i. Second bullet: "...at 2°-8°C (36°-46°F). Do not freeze"
      ii. Third bullet: "...at room temperature, 20°-25°C (68°-77°F), in an..."
   b. How to use Calcitonin-Salmon Nasal Spray, Step 5, third sentence: "...at room temperature (20°-25°C [68°-77°F]) in the..."

5. **INFORMATION FOR THE PATIENT**
   a. *How do I use calcitonin-salmon nasal spray?* Add as the last 2 sentence: "You should keep track of the number of doses used from the bottle. **After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.**"
   b. *Possible Side Effects*, Bullet one: "Nasal symptoms such..." [delete comma]

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Skin testing protocol.

SKIN TESTING

There have been rare reports of systemic allergic reactions to ~~Miacalcin.~~ Calcitonin-salmon nasal spray.

Skin testing is not required prior to treatment with ~~Miacalcin Nasal Spray~~ calcitonin-salmon nasal spray; however, skin testing should be considered in patients with suspected sensitivity to calcitonin. These typically would be people who have a history of numerous allergies and, therefore, the potential to be more sensitive to any medication.

This ~~protocol has been devised for Novartis by the American Academy of Allergy and Immunology. It~~ is an in vitro protocol similar to others used for testing for allergic drug reactions. The testing physician should understand the procedures of the protocol, be able to carry out the appropriate controls and interpret the skin reactions. The physician may also choose to refer these patients to an allergist for testing.

PROTOCOL

1. Make sure the patient has not used oral antihistamines or any other oral or injectable agent with antihistamine properties for at least three days. Exceptions would be for hydroxyzine (5 days) and astemizole (6 weeks).

2. Prepare a 1:100 and a 1:1000 dilution of ~~the Miacalcin Injection~~ calcitonin-salmon injection solution using normal saline. Also have available solutions for controls including normal saline (negative control) and histamine (1 mg/ml) (positive control).

3. A prick puncture test should first be performed with the saline control and the positive histamine control. The test should be read at 15 minutes after application. The saline control should be negative, i.e. minimal wheal and no erythema. The positive control reaction should demonstrate some degree of wheal and erythema. If the saline control is negative and the histamine control is positive, interpretation of the skin testing with ~~the Miacalcin~~ is valid.

4. A prick puncture test is then applied using the concentrated, undiluted ~~Miacalcin~~ Calcitonin-salmon injection solution. The prick puncture test is negative if the reaction is equal to or less than the control. Calcitonin-Salmon injection solution

Calcitonin-salmon injectable solution

Calcitonin-salmon

calcitonin-salmon injection solution

5. An intradermal test using 0.02 ml of 1:1000 dilution of ~~the Miacalcin~~ is then performed along with a saline control. Observe the sites for 15 minutes. If the ~~Miacalcin~~ reaction and the saline control reaction are negative, an intradermal test using the 1:100 ~~Miacalcin solution~~ is performed and the injection site observed for 15 minutes. If this reaction is negative, it is unlikely that the patient will exhibit a systemic allergic reaction to the ~~Miacalcin~~ when administered. To be cautious, while under observation by a physician, 0.05 ml of the ~~Miacalcin~~ injectable concentrate solution can be administered subcutaneously and the patient observed for 10 minutes. If there is no adverse reaction, 0.1 ml of the concentrate solution can be administered and the patient observed for 10 minutes. If no reaction is noted, the remaining portion of the standard 0.5 ml dose (i.e. .35 ml) can be administered and the patient observed for 10 minutes. Calcitonin-salmon

Calcitonin-salmon nasal spray

6. A positive skin test response is when the reaction to the prick test has a wheal diameter greater than 3 mm larger than the diluent control or when the intradermal test has a wheal diameter greater than 7 mm larger than the diluent control. A positive response to ~~the Miacalcin~~ should make one suspect the possibility that the patient has an allergy to ~~Miacalcin.~~ Calcitonin-salmon injection solution

Calcitonin-salmon nasal spray.

REFERENCES

Patterson et al; Drug Allergy and Protocols for Management of Drug Allergies, 2nd Edition, Oceanside Publications, 1995.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			X
Is the scoring configuration different than the RLD?			X
			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313). The most recently approved labeling is NDA 20-313/S-023; Approved August 22, 2003; FPL provided in the December 17, 2003 submission (refer to EDR); FPL AR May 26, 2004. NDA 20-313/S-023 provides for a larger vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses. The generic ANDA is available as 2 mL bottles (2 bottles per carton). Therefore, the generic ANDA's labels and labeling reflects the delivery of the 14 doses.

- In Novartis insert labeling, Warnings, Allergic Reactions section, the practitioner is referrerd to the Medical Services Department of Novartis Pharmaceuticals Corporation for a detailed skin testing protocol. I obtained the protocol from Novartis on June 2, 2004. Based on a conversation with team leader John Grace on June 3, 2004, we need to ask the generic firm to provide the skin protocol as well.
- The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. This education program is mentioned in the "Patient Instructions" labeling only ("For more information on Miacalcin (calcitonin-salmon) Nasal Spray and

how to assemble it, and to enroll in the Miacalcin Nasal Spray Patient Education Program, please call 1800-347-BONE"), not in the physician insert. Based on Randy Hedin's (RLD project manager) email, the program was not reviewed by the division as part of the approval. Based on an email from team leader John Grace on April 14, 2003, if the program was not a condition for approval and appears to be promotional material, then ANDAs should not be required to submit.

- Novex Pharma Patient's Instructions for Use and Information for the Patient come as a perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31,2015	U-227
020313	002	5759565	MAR 31,2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.2, pg 566]

4. CONTAINER/CLOSURE

Package Size 2 mL
Bottle: 3 mL (b) (4) clear type I glass
Nasal Spray Pump: Nasal Spray Pump with white actuator and cap
[Vol. A1.2, pg. 686]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. Note: In the September 11, 2002 submission, Novex revised the formulation to remove (b) (4) (in order to be Q1/Q2 to the innovator.)
Note: In NDA 20-313/S-018, Novartis deleted (b) (4).

6. PACKAGING CONFIGURATIONS

RLD: Two 2-mL vials and applicators per carton; approved in NDA 20-313/S-023 3.7 mL of solution to deliver 30 dose (one bottle with applicator per carton)
ANDA: Two 2-mL bottles per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately). [Chem. Review #1]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: N/A

RLD: [For 14 dose bottles]
Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.
Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36° F to 46° F (2° C to 8° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36° F to 46° F (2° C to 8° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.

ANDA: Container & Carton-same as rld
Insert- Store bottle in use at room temperature in an upright position for up to 30 days. Each bottle contains at least 14 doses. Store second bottle in refrigerator until ready to use. Protect from freezing. Discard all unrefrigerated bottles after 30 days.

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:
Found deficient March 30, 2004.

Date of Review: June 3, 2004 Date of Submission: April 23, 2003 and February 25, 2004

Primary Reviewer: Ruby Wu RWu Date: 6/3/04

Team Leader: John Grace Date: 6/3/04

cc:

ANDA: 76-396
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-396
Date of Submissions: July 29, 2004
Applicant's Name: Novex Pharma (Currently Apotex Inc.)
Established Name: Calcitonin-Salmon Nasal Spray, 200 IU/spray

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Container Labels: (2mL bottles/14 doses per bottle)
  Satisfactory in FPL as of July 29, 2004 submission.
  (Vol. 5.1 and
  \\Cdsesubogd1\n76396\N_000\2004-07-29\labeling\cali_naso_200iuspray_lbl_207258.pdf.pdf)

- Carton: (2 X 2mL bottles)
  Satisfactory in FPL as of July 29, 2004 submission.
  (Vol. 5.1 and
  \\Cdsesubogd1\n76396\N_000\2004-07-29\labeling\cali_naso_200iuspray_ctn_207258.pdf.pdf)

- Professional Package Insert Labeling:
  Satisfactory in FPL as of July 29, 2004 submission.
  (Vol. 5.1 and
  \\Cdsesubogd1\n76396\N_000\2004-07-29\labeling\cali_naso_200iuspray_ins_207258.pdf.pdf)

- Skin Testing Protocol
  Satisfactory in FPL as of July 29, 2004 submission.
  (Vol. 5.1 p. 11)

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Mialcalcin® Nasal Spray
- NDA Number: 20-313
- NDA Drug Name: Mialcalcin® Nasal Spray
- NDA Firm: Novartis Pharmaceuticals Corporation
- Date of Approval of NDA Insert and supplement #: August 22, 2003/S-023
- Has this been verified by the MIS system for the NDA? yes
- Was this approval based upon an OGD labeling guidance? no
- Basis of Approval for the Container Labels: side-by-side
- Basis of Approval for the Carton Labeling: side-by-side

PATENTS/EXCLUSIVITIES

Patent Data: NDA 20-313

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5733569	***MAR 31,2015***	U-227	**NASAL ADMINISTRATION**	IV	None
5759565	***MAR 31,2015***			IV	None

Exclusivity Data: NDA 20-313

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	NA
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313). The most recently approved labeling is NDA 20-313/S-023; Approved August 22, 2003; FPL provided in the December 17, 2003 submission (refer to EDR); FPL AR May 26, 2004. NDA 20-313/S-023 provides for a larger vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses. The generic ANDA is available as 2 mL bottles (2 bottles per carton). Therefore, the generic ANDA's labels and labeling reflects the delivery of the 14 doses.

- In Novartis insert labeling, Warnings, Allergic Reactions section, the practitioner is referrerd to the Medical Services Department of Novartis Pharmaceuticals Corporation for a detailed skin testing protocol. I obtained the protocol from Novartis on June 2, 2004. Based on a conversation with team leader John Grace on June 3, 2004, we need to ask the generic firm to provide the skin protocol as well.
- The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. This education program is mentioned in the "Patient Instructions" labeling only ("For more information on Miacalcin (calcitonin-salmon) Nasal Spray and

how to assemble it, and to enroll in the Miacalcin Nasal Spray Patient Education Program, please call 1800-347-BONE"), not in the physician insert. Based on Randy Hedin's (RLD project manager) email, the program was not reviewed by the division as part of the approval. Based on an email from team leader John Grace on April 14, 2003, if the program was not a condition for approval and appears to be promotional material, then ANDAs should not be required to submit.

- Novex Pharma Patient's Instructions for Use and Information for the Patient come as a perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31 2015	U-227
020313	002	5759565	MAR 31 2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.2, pg 566]

4. CONTAINER/CLOSURE

Package Size 2 ml
Bottle: 3 mL (b) (4) clear type I glass
Nasal Spray Pump: Nasal Spray Pump with white actuator and cap
[Vol. A1.2, pg. 686]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. Note: In the September 11, 2002 submission, Novex revised the formulation to remove (b) (4) (in order to be Q1/Q2 to the innovator.)
Note: In NDA 20-313/S-018, Novartis deleted (b) (4)

6. PACKAGING CONFIGURATIONS

RLD: Two 2-mL vials and applicators per carton; approved in NDA 20-313/S-023 3.7 mL of solution to deliver 30 dose (one bottle with applicator per carton)
ANDA: Two 2-mL bottles per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately). [Chem. Review #1]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: N/A

RLD: [For 14 dose bottles]
Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.
Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36° F to 46° F (2° C to 8° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36° F to 46° F (2° C to 8° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.

ANDA: Container & Carton-same as rld
Insert- Store bottle in use at room temperature in an upright position for up to 30 days. Each bottle contains at least 14 doses. Store second bottle in refrigerator until ready to use. Protect from freezing. Discard all unrefrigerated bottles after 30 days.

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:
Found deficient March 30, 2004.

Date of Review: September 7, 2004 Date of Submission: July 29, 2004

Primary Reviewer: Postelle Birch Date: 9/7/2004

Team Leader: John Grace Date: 9/9/2004

cc:
ANDA: 76-396
DUP/DIVISION FILE
HFD-613/PBirchforRWu/JGrace (no cc)
V:\FIRMSNZ\NOVEX\LTRS&REV\76396.AP.L.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-396
Date of Submission:	January 31, 2005 (addition of 30 doses/bottle size)
Applicant's Name:	Apotex Inc. (formerly Novex Pharma)
Established Name:	Calcitonin-Salmon Nasal Spray, 200 IU/spray

Labeling Deficiencies:

1. Container Labels (2 mL bottle [14 doses per bottle] and 3.7 mL bottle [30 doses per bottle])
   Principal display panel: Add "14 dose bottle" to the 2 mL bottle and "30 dose bottle" to the 3.7 mL bottle.

2. Carton: (2 X 2 mL bottles and 1 x 3.7 mL bottle)
   2 x 2 mL bottle carton: Satisfactory as of the July 29, 2004 submission.
   1 x 3.7 mL bottle carton:
   a. "3.7 mL bottle" [add "bottle"]
   b. Principal display panel: Increase the prominence of "30 Doses Per Bottle"

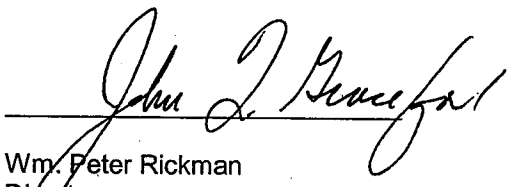
3. COMBINATION Profession Insert, Patient Instructions for Use and Patient Information
   2 mL bottle: Satisfactory as of the July 29, 2004 submission.
   3.7 mL bottle: Satisfactory as of the January 31, 2005 submission.

4. Skin Testing Protocol
   Satisfactory as of the July 29, 2004 submission.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 28 (checked on 5/10/05)		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			X
Is the scoring configuration different than the RLD?			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

Emailed to chemist 5/10/05

In the January 31, 2005 amendment, the firm added 30 doses per bottle to their ANDA. Please note the storage recommendation:

14 doses: store bottle in use at room temperature...[for up to 30 days] in an upright position

30 doses: store bottle in use at room temperature...[for up to 35 days] in an upright position.

Did the firm provide stability data to support?

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313). The most recently approved labeling is NDA 20-313/S-023; Approved August 22, 2003; FPL provided in the December 17, 2003 submission (refer to EDR); FPL AR May 26, 2004. NDA 20-313/S-023 provides for a larger vial containing 3.7 mL of solution to deliver 30 doses instead of the currently approved 14 doses.

In the January 31, 2005 amendment, Apotex added the 30 dose bottle to their ANDA. The review of the labels and labeling for Apotex's 14 dose bottle and 30 dose bottle are both based on NDA 20-313-S-023. However, the labels and labeling for the 14 dose bottle have been revised to reflect the delivery of 14 doses.

- In Novartis insert labeling, Warnings, Allergic Reactions section, the practitioner is referrerd to the Medical Services Department of Novartis Pharmaceuticals Corporation for a detailed skin testing protocol. I obtained the protocol from Novartis on June 2, 2004. Based on a conversation with team leader John Grace on June 3, 2004, we asked the generic firm to provide the skin protocol as well.
- The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. This education program is mentioned in the "Patient Instructions" labeling only ("For more information on Miacalcin (calcitonin-salmon) Nasal Spray and how to assemble it, and to enroll in the Miacalcin Nasal Spray Patient Education Program, please call 1800-347-BONE"), not in the physician insert. Based on Randy Hedin's (RLD project manager) email, the program was not reviewed by the division as part of the approval. Based on an email from team leader John Grace on April 14, 2003, if the program was not a condition for approval and appears to be promotional material, then ANDAs should not be required to submit.
- Novex Pharma Patient's Instructions for Use and Information for the Patient come as a perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31,2015	U-227
020313	002	5759565	MAR 31,2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Apotex Inc. (formerly Novex Pharma)
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.2, pg 566]

4. CONTAINER/CLOSURE
Package Size 2 mL and 3.7 mL
Bottle: clear type I glass
Nasal Spray Pump: Nasal Spray Pump with white actuator and cap
[Vol. A1.2, pg. 686]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. Note: In the September 11, 2002 submission, Novex revised the formulation to remove (b) (4) (in order to be Q1/Q2 to the innovator.)
Note: In NDA 20-313/S-018, Novartis deleted (b) (4).

6. PACKAGING CONFIGURATIONS

RLD: Two 2-mL vials and applicators per carton; approved in NDA 20-313/S-023 3.7 mL of solution to deliver 30 dose (one bottle with applicator per carton)
ANDA: Two 2-mL bottles per carton and one 3.7 mL bottle per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately). [Chem. Review #1]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: N/A
RLD: [For 14 dose bottles]
Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.
Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36 ° F to 46 ° F (2 ° C to 8 ° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36 ° F to 46 ° F (2 ° C to 8 ° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.
[For 30 dose bottles]: same as above except "...(for up to 35 days...)
ANDA: same as RLD. Refer to Note to the chemist

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:
Pending as of 5/10/05

Date of Review: May 10, 2005 Date of Submission: January 31, 2005

Primary Reviewer: Ruby Wu RWu Date: 5/10/05

Team Leader: John Grace Date: John Z Grace 5-10-2005

cc:

ANDA: 76-396
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\NOVEX\LTRS&REV\76396.na4.L.doc
Review

dev-fil

This review supersedes the approval summary based on the 7/29/04 amendment

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-396
Date of Submission: May 18, 2005 (amendment)
Applicant's Name: Apotex Inc. (formerly Novex Pharma)
Established Name: Calcitonin-Salmon Nasal Spray, 200 IU/spray

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes

1. **Container Labels (2 mL bottle [14 doses per bottle] and 3.7 mL bottle [30 doses per bottle])**
   2 mL bottle: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesubogd1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_lbl_204604.pdf

   3.7 mL bottle: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesubogd1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_lbl_227893.pdf

2. **Carton: (2 X 2 mL bottles and 1 x 3.7 mL bottle)**
   2 x 2 mL bottle carton: Satisfactory in final print as of the July 29, 2004 e-submission.
   \\Cdsesubogd1\n76396\N_000\2004-07-29\LABELING\cali_naso_200iuspray_ctn_207258.pdf.pdf

   1 x 3.7 mL bottle carton: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesubogd1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_ctn_227895.pdf

3. **COMBINATION Profession Insert, Patient Instructions for Use and Patient Information**
   2 mL bottle: Satisfactory in final print as of the July 29, 2004 e-submission.
   \\Cdsesubogd1\n76396\N_000\2004-07-29\LABELING\cali_naso_200iuspray_ins_204608.pdf.pdf

   3.7 mL bottle: Satisfactory in final print as of the January 31, 2005 e-submission.
   \\Cdsesubogd1\n76396\N_000\2005-01-31\cali_naso_200iu_spry_ins_TBD3_7.pdf
   There is one note to the chemist

4. **Skin Testing Protocol**
   Satisfactory in final print as of July 29, 2004 submission. (Vol. 5.1 p. 11)

Revisions needed post-approval? No.

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Mialcalcin® Nasal Spray
NDA Number: 20-313
NDA Drug Name: Mialcalcin® Nasal Spray
NDA Firm: Novartis Pharmaceuticals Corporation
Date of Approval of NDA Insert and supplement #: August 22, 2003/S-023
Has this been verified by the MIS system for the NDA? yes
Was this approval based upon an OGD labeling guidance? no
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Carton Labeling: side-by-side

PATENTS/EXCLUSIVITIES

Patent Data: NDA 20-313

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5733569	MAR 31,2015	U-227	NASAL ADMINISTRATION	IV	None
5759565	MAR 31,2015			IV	None

Exclusivity Data: NDA 20-313

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 28 (checked on 7/7/05)		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

Emailed to chemist 5/10/05

In the January 31, 2005 amendment, the firm added 30 doses per bottle to their ANDA. Please note the storage recommendation:

14 doses: store bottle in use at room temperature...[for up to 30 days] in an upright position

30 doses: store bottle in use at room temperature...[for up to 35 days] in an upright position.

Did the firm provide stability data to support?

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313). The most recently approved labeling is NDA 20-313/S-023(Approved August 22, 2003; FPL provided in the December 17, 2003 submission (refer to EDR); FPL AR May 26, 2004.) NDA 20-313 was originally approved with 2 mL bottles (2 bottles per carton; each bottle delivers 14 doses). NDA 20-313/S-023 provides for a larger vial containing 3.7 mL of solution to deliver 30 doses. *There is one labeling supplement (SLR-021) in approvable status as of 7/7/05.*

In the January 31, 2005 amendment, Apotex added the 30 dose bottle to their ANDA. The review of the labels and labeling for Apotex's 14 dose bottle and 30 dose bottle are both based on NDA 20-313-S-023. However, the labels and labeling for the 14 dose bottle have been revised to reflect the delivery of 14 doses.

In Novartis insert labeling, Warnings, Allergic Reactions section, the practitioner is referrerd to the Medical Services Department of Novartis Pharmaceuticals Corporation for a detailed skin testing protocol. I obtained the protocol from Novartis on June 2, 2004. Based on a conversation with team leader John Grace on June 3, 2004, we asked the generic firm to provide the skin protocol as well.

The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. This education program is mentioned in the "Patient Instructions" labeling only ("For more information on Miacalcin (calcitonin-salmon) Nasal Spray and how to assemble it, and to enroll in the Miacalcin Nasal Spray Patient Education Program, please call 1800-347-BONE"), not in the physician insert. Based on Randy Hedin's (RLD project manager) email, the program was not reviewed by the division as part of the approval. Based on an email from team leader John Grace on April 14, 2003, if the program was not a condition for approval and appears to be promotional material, then ANDAs should not be required to submit.

Novex Pharma Patient's Instructions for Use and Information for the Patient come as a perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31,2015	U-227
020313	002	5759565	MAR 31,2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [Vol. A1.2, pg 566]
Apotex Inc. (formerly Novex Pharma)
380 Elgin Mills Road East
Richmond Hill, Ontario Canada L4C 5H2

4. CONTAINER/CLOSURE [Vol. A1.2, pg. 686]
Package Size 2 mL and 3.7 mL
Bottle: clear type I glass
Nasal Spray Pump: Nasal Spray Pump with white actuator and cap

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling is consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. Note: In the September 11, 2002 submission, Novex revised the formulation to remove (b) (4) (in order to be Q1/Q2 to the innovator.)
Note: In NDA 20-313/S-018, Novartis deleted (b) (4)

6. PACKAGING CONFIGURATIONS
RLD: Two 2-mL vials and applicators per carton; approved in NDA 20-313/S-023 3.7 mL of solution to deliver 30 dose (one bottle with applicator per carton)
ANDA: Two 2-mL bottles per carton and one 3.7 mL bottle per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately).

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP: N/A
RLD: [For 14 dose bottles]
Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.
Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36 ° F to 46 ° F (2 ° C to 8 ° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36 ° F to 46 ° F (2 ° C to 8 ° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.
[For 30 dose bottles]: same as above except "...(for up to 35 days...)
ANDA: same as RLD. **Refer to Note to the chemist**

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:
Pending as of 7/7/05

Date of Review: July 7, 2005 Date of Submission: May 18, 2005 (amendment)

Primary Reviewer: Ruby Wu Date: 7/7/05

Team Leader: John Grace Date: 7/8/05

cc: ANDA: 76-396
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\NOVEX\LTRS&REV\76396.AP2.L.doc
Review

This review supersedes the approval summary signed-off July 8, 2005

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-396
Date of Submission: February 23, 2006 (amendment)
Applicant's Name: Apotex Inc. (formerly Novex Pharma)
Established Name: Calcitonin-Salmon Nasal Spray, 200 IU/spray

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes

1. **Container Labels (2 mL bottle [14 doses per bottle] and 3.7 mL bottle [30 doses per bottle])**
   2 mL bottle: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesub1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_lbl_204604.pdf

   3.7 mL bottle: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesub1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_lbl_227893.pdf

2. **Carton: (2 X 2 mL bottles and 1 x 3.7 mL bottle)**
   2 x 2 mL bottle carton: Satisfactory in final print as of the July 29, 2004 e-submission.
   \\Cdsesub1\n76396\N_000\2004-07-29\LABELING\cali_naso_200iuspray_ctn_207258.pdf.pdf

   1 x 3.7 mL bottle carton: Satisfactory in final print as of the May 18, 2005 e-submission.
   \\Cdsesub1\n76396\N_000\2005-05-18\Labeling\cali_naso_200iu_spry_ctn_227895.pdf

3. **COMBINATION Profession Insert, Patient Instructions for Use and Patient Information**
   2 mL bottle: Satisfactory in final print as of the February 23, 2006 e-submission.
   \\Cdsesub1\n76396\N_000\2006-02-23\labeling\cali_naso_2ml_ins_204608.pdf

   3.7 mL bottle: Satisfactory in final print as of the February 23, 2006 e-submission.
   \\Cdsesub1\n76396\N_000\2006-02-23\labeling\cali_naso_3_7ml_ins_TBD.pdf
   ****There is one note to the chemist****

4. **Skin Testing Protocol**
   Satisfactory in final print as of July 29, 2004 submission. (Vol. 5.1 p. 11)

Revisions needed post-approval? No.

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Mialcalcin® Nasal Spray
NDA Number: 20-313
NDA Drug Name: Mialcalcin® Nasal Spray
NDA Firm: Novartis Pharmaceuticals Corporation
Date of Approval of NDA Insert and supplement #: 20-313/S-021 approved January 6, 2006
Has this been verified by the MIS system for the NDA? yes
Was this approval based upon an OGD labeling guidance? no
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Carton Labeling: side-by-side

PATENTS/EXCLUSIVITIES

Patent Data: NDA 20-313 (checked 3/9/06)

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5733569	MAR 31,2015	U-227	NASAL ADMINISTRATION	IV	None
5759565	MAR 31,2015			IV	None

Exclusivity Data: NDA 20-313

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

NOTES/QUESTIONS TO THE CHEMIST:
Emailed to chemist 5/10/05
In the January 31, 2005 amendment, the firm added 30 doses per bottle to their ANDA. Please note the storage recommendation:
14 doses: store bottle in use at room temperature...[for up to 30 days] in an upright position
30 doses: store bottle in use at room temperature...[for up to 35 days] in an upright position.
Did the firm provide stability data to support?

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Miacalcin® Nasal Spray by Novartis Pharmaceuticals Corporation (NDA 20-313). The most recently approved labeling is NDA 20-313/S-021 approved January 6, 2006 and this supplement provided for revised geriatric use language.

NDA 20-313 was originally approved with 2 mL bottles (2 bottles per carton; each bottle delivers 14 doses). NDA 20-313/S-023 provided for a larger vial containing 3.7 mL of solution to deliver 30 doses.

In the January 31, 2005 amendment, Apotex added the 30 dose bottle to their ANDA. The review of the labels and labeling for Apotex's 14 dose bottle and 30 dose bottle are both based on NDA 20-313/S-021. However, the labels and labeling for the 14 dose bottle have been revised to reflect the delivery of 14 doses.

In Novartis insert labeling, Warnings, Allergic Reactions section, the practitioner is referred to the Medical Services Department of Novartis Pharmaceuticals Corporation for a detailed skin testing protocol. I obtained the protocol from Novartis on June 2, 2004. Based on a conversation with team leader John Grace on June 3, 2004, we asked the generic firm to provide the skin protocol as well.

The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. This education program is mentioned in the "Patient Instructions" labeling only ("For more information on Miacalcin (calcitonin-salmon) Nasal Spray and how to assemble it, and to enroll in the Miacalcin Nasal Spray Patient Education Program, please call 1800-347-BONE"), not in the physician insert. Based on Randy Hedin's (RLD project manager) email, the program was not reviewed by the division as part of the approval. Based on an email from team leader John Grace on April 14, 2003, if the program was not a condition for approval and appears to be promotional material, then ANDAs should not be required to submit.

Novex Pharma Patient's Instructions for Use and Information for the Patient come as a perforated attachment to the Prescribing Information insert, while the Novartis Patient instructions and Information for the Patient are formatted as a separate booklet. (Vol A1.1 pg. 36)

2. PATENTS/EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 020313 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020313	002	5733569	MAR 31,2015	U-227
020313	002	5759565	MAR 31,2015	

Exclusivity Data

There is no unexpired exclusivity for this product.

Novex provided a PIII certification to patents '569 and '565 in the original submission. [Vol. A1.1, pg10]
In the 9/25/02 submission, Novex revised the Patent certification from PIII to PIV.
In the 11/18/02 submission, Novex notified the FDA that Novartis has filed civil action against Novex, Civil Action No. 02 CV 8917 [Vol. B1.10]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [Vol. A1.2, pg 566]
Apotex Inc. (formerly Novex Pharma)
380 Elgin Mills Road East
Richmond Hill, Ontario Canada L4C 5H2

4. CONTAINER/CLOSURE [Vol. A1.2, pg. 686]
Package Size 2 mL and 3.7 mL
Bottle: clear type I glass
Nasal Spray Pump: Nasal Spray Pump with white actuator and cap

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling is consistent with the composition statement found in Vol. B1.1, Sep. 11, 02 amendment, attachment 3. Note: In the September 11, 2002 submission, Novex revised the formulation to remove [redacted] (b) (4) (in order to be Q1/Q2 to the innovator.)
Note: In NDA 20-313/S-018, Novartis deleted [redacted] (b) (4)

6. PACKAGING CONFIGURATIONS
RLD: Two 2-mL vials and applicators per carton; approved in NDA 20-313/S-023 3.7 mL of solution to deliver 30 dose (one bottle with applicator per carton)
ANDA: Two 2-mL bottles per carton and one 3.7 mL bottle per carton
The configuration of the CCS used by Novex (one piece, assembled) is slightly different from that used by the innovator (bottles and pumps are supplied separately).

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP: N/A
RLD: [For 14 dose bottles]
Container-Store in refrigerator until opened, then at room temperature in an upright position. Protect from freezing.
Carton Front & Back- Refrigerate until opened.
Carton Side- Store bottle in use at room temperature (for up to 30 days) in an upright position. Store second bottle in refrigerator at 36 ° F to 46 ° F (2 ° C to 8 ° C) until ready to use. Protect from freezing.
Insert-Store unopened in refrigerator between 36 ° F to 46 ° F (2 ° C to 8 ° C). Protect from freezing. Opened bottles must be maintained at room temperature (for up to 30 days) in an upright position. Each bottle, after priming, contains 14 doses.
[For 30 dose bottles]: same as above except "...(for up to 35 days...)
ANDA: same as RLD. **Refer to Note to the chemist**

8. PRODUCT DESCRIPTION
The product has been accurately described in the HOW SUPPLIED section of the insert.

9. BIOAVAILABILITY/BIOEQUIVALENCE:
12/20/2005 - Bio deficiencies given to document room for faxing/bff

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Date of Review: March 9, 2006 Date of Submission: February 23, 2006 (amendment)

Primary Reviewer: Ruby Wu RW Date: 3/9/06

Team Leader: John Grace John J Grace Date: 3.9.06

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cc: ANDA: 76-396
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\NOVEX\LTRS&REV\76396.AP3.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

CHEMISTRY REVIEWS

#1

ANDA 76-396

Calcitonin-Salmon Nasal Spray
(200 IU/Spray)

NOVEX PHARMA
CANADA

Bing Cai, Ph. D.

Division of Chemistry I
Office of Generic Drugs

OCTOBER 2002

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **76-396**

2. REVIEW #: **1**

3. REVIEW DATE: **October 2, 2002**

4. REVIEWER: **Bing Cai, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NOVEX	
Original Submission	08-Apr-2002
FDA	
Refuse to Filling	11-Jun-2002
Acceptable for Filling as 17-Jul-2002	16-Sep-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission/By Apotex	08-Apr-2002
NC re Q_1/Q_2	15-Jul-2002
NC re Q_1/Q_2	12-Sep-2002
Tel Amendment	23-Sep-2002
NC re Patent Certification (P. III→P. IV)	25-Sep-2002
NC re Patent Infringement Notice	18-Nov-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Novex Pharma
Address:	380 Elgin Mills Road East Richmond Hill, Ontario, Canada L4C 5H2
Representative:	Dawn Culp
Telephone/FAX:	905-884-2050/905-884-9876

Chemistry Review Data Sheet

US Agent:	Apotex Corp.
Address:	50 Lakeview Parkway, Suite 127 Vernon Hills, IL 60061
Representative:	Marcy Macdonald
Telephone/FAX:	847-573-9999/847-573-1001

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Calcitonin-Salmon Nasal Spray

9. LEGAL BASIS FOR SUBMISSION: 505(j)(2)(A)(vii)(**IV**)*

Reference Product: Miacalcin® Nasal Spray
Manufacturer: Novartis (NDA 20-313)

	Patent #/Expiration Date	Use Code
Patent	5733569 (31-Mar-2015) 5759565 (31-Mar-2015)	U-227
Exclusivity	None	None

* The original submitted Paragraph III Certification is revised to a Paragraph IV Certification in an amendment dated September 25, 2002.

10.PHARMACOL. CATEGORY:

Lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption.

11. DOSAGE FORM: Solution/Nasal Spray

12. STRENGTH/POTENCY: 200 IU/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2 [Disulfide Bridge: 1-7]

$C_{145}H_{240}N_{44}O_{48}S_2$; MW=3431.9 (*CAS 47931-89-1*)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
1 2 3 4 5 6 7 8 9

Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-
10 11 12 13 14 15 16 17 18 19

Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
20 21 22 23 24 25 26 27 28 29

Gly-Thr-Pro-NH_2
30 31 32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	inadequate	10/31/02	By Cai HFD-620
	III			4	N/A		
	III			6	N/A		

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 –Type 1 DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application; 5 – Authority to reference not granted 6 – DMF not available; 7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	--	
EES	Pending	--	
Methods Validation	Not to be issued at this cycle	--	
Labeling	Pending	--	
Bioequivalence/Waiver	Pending	--	
EA	N/A	--	
Radiopharmaceutical	N/A	--	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-396

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The ANDA is not approvable pending clarification of minor chemistry issues, including raw material controls, API manufacturing control (DMF deficiencies), drug product manufacturing process, container/closure system, controls of the drug product at release and stability (specifications and test methods). The Bioequivalence Studies and Labeling are pending review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug product, Calcitonin-Salmon Nasal Spray is labeled for nasal use. The drug product is packaged in 2 mL fill glass bottles with a meter pump. The pumps, following priming, will deliver 0.09 mL of solution each spray. Each bottle contains at least 14 doses. The information provided for the Nasal Pump used for this drug product is found incomplete at this time.

- There are no USP monographs for Calcitonin-Salmon (drug substance or drug product). NOVEX has developed its own in-house methods for drug product and drug substance testing. There are several issues regarding the DS/DP specifications and test methods that need to be resolved. The "Spray Pattern" specification is (b) (4) and needs to be (b) (4). The "Spray Pattern" study is still pending for bio-review. All related DS/DP test methods will be evaluated by the FDA laboratories when all issues are solved.

- NOVEX's drug product manufacturing process is generally acceptable, except the firm should provide additional information (from process development) for (b) (4) (b) (4) during the manufacturing. The firm will also be asked to provide clarification for some other minor issues regarding the (b) (4) process.

- Based on results generated from their 3-months stability data under the accelerated conditions, this drug product has been found very stable. No significant trends for assay drop (or increase) were found. No significant trends of increase for each individual related peptide or total related peptides were found. There are not enough RT stability data generated at this time (only up to 3-months). The available accelerated stability data support a 24 months expiration dating period.

- The [redacted] (b) (4) is supplied by [redacted] (b) (4) (DMF [redacted] (b) (4)). The DMF [redacted] (b) (4) was reviewed and a deficiency letter has been issued and pending a response from the DMF holder. NOVEX's [redacted] (b) (4) specifications are found not acceptable at this time.

B. Description of How the Drug Product is Intended to be Used

- The recommended dose for Calcitonin-Salmon Nasal Spray is one spray per day.

- Stored unopened bottles in refrigerator between 36-46 ^{0}F (2-8 ^{0}C). protect from freezing. Stored opened bottles at RT in an upright position for up to 30 days. Discard all unrefrigerated bottles after 30 days.

- The expiration for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

MINOR Chemistry Issues:

- Controls for DS/DP;
- API and DP manufacturing and;
- Container Closure System.

Pending Labeling review;
Pending Method Validation;
Pending Bio review;
Pending EES.

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

12/30/02

HFD-620/B.Cai,Ph.D/11/21/02, 12/21/02, 12/29/02
HFD-620/S.Liu,PhD/
HFD-620/W.Pamphile, PM/
V:\FIRMSNZ\NOVEX\LTRS&REV\76396cr1.revision.doc
F/T by:

C. CC Block

ANDA 76-396
ANDA DUP
DIV FILE
Field Copy

Following this page, 27 pages withheld in full (b)(4)- CCI/TS

32. LABELING Pending

Items Reviewed by Chemist: Satisfactory

1. Description Section
    a. Structures: Satisfactory
    b. Chemical names: Satisfactory
    c. Empirical formulas: Satisfactory
    d. Name of the inactives: pending (b) (4)
    e. Physical and Chemical properties of DS: Satisfactory

2. How Supplied Section
    a. Packaging: metered dose solution in 2 mL fill glass bottles. The pumps, following priming, will deliver 0.09 mL of solution. Each bottle contains at least 14 doees.

    b. Storage Conditions: Satisfactory
        - Store at (b) (4) 36-46° F (2-8 °C). Protected from freezing.
        - Stored bottles at RT in an upright position for up to 30 days. Discard all unrefrigerated bottles after 30 days.

NOTES/QUESTIONS FROM THE LABELING REVIEW:

Not available, Labeling review is pending

33. ESTABLISHMENT INSPECTION Pending

34. BIOEQUIVALENCE Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm stated that they are subject to a categorical exclusion (pages 3653/3654). They also stated that they are in compliance with federal, state, and local environmental laws.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-396 APPLICANT: NOVEX Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/Spray

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

Following this page, 3 pages withheld in full (b)(4)- CCI/TS

18. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

3. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

4. We require an acceptable Methods Validation to support the ANDA and will schedule the study after the test method issues are resolved. Please provided a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approve prior to its completion.

5. Please provide any additional long term stability data that may be available.

6. We acknowledge the submission of the Master Packaging Order in your amendment dated July 15, 2002. Please be advised that all packaging instructions should be included in the Master Formula.

7. DMF [redacted] (b) (4) for the [redacted] (b) (4) is currently under review by another Division in the Center.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-396
ANDA DUP 76-396
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/B. Cai, Ph.D/11/21/02, 12/23/02, 12/29/02
HFD-627/S.Liu,PhD/ 12/30/02
HFD-617/W.Pamphile, PM
V:\FIRMSNZ\NOVEX\LTRS&REV\76396CR1.REVISION.DOC
F/T by:

TYPE OF LETTER: NOT APPROVABLE - MINOR

#2

ANDA 76-396

Calcitonin-Salmon Nasal Spray
(200 IU/Spray)

NOVEX PHARMA

Bing Cai, Ph. D.

Division of Chemistry I
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **76-396**

2. REVIEW #: **2**

3. REVIEW DATE: **March 31, 2004**
   July 14, 2004 (revised)

4. REVIEWER: **Bing Cai, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NOVEX	
Original Submission	08-Apr-2002
NC re Q_1/Q_2	15-Jul-2002
Tel Amendment	23-Sep-2002
New Correspondence	28-Mar-2004
Labeling Amendment	23-April-2004
New Correspondence	9-Jun-2004
FDA	
Refuse to Filling	11-Jun-2002
Acceptable for Filling as 17-Jul-2002	16-Sep-2002
CMC NA letter	3-Jan-2003
T-con	10-Mar-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (T-Con request)	11-Feb-2004
Amendment	25-Feb-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Novex Pharma
Address:	380 Elgin Mills Road East Richmond Hill, Ontario, Canada L4C 5H2
Representative:	Dawn Culp
Telephone/FAX:	905-884-2050/905-884-9876
US Agent:	Apotex Corp.
Address:	616 Heathrow Drive Lincolnshire, IL 60069
Representative:	Marcy Macdonald
Telephone/FAX:	847-821-8005/847-353-2982

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Calcitonin-Salmon Nasal Spray

9. LEGAL BASIS FOR SUBMISSION: 505(j)(2)(A)(vii)(**IV**)*

See CR#1 (*The original submitted Paragraph III Certification is revised to a Paragraph IV Certification in an amendment dated September 25, 2002).

Reference Product:	Miacalcin® Nasal Spray
Manufacturer:	Novartis (NDA 20-313)

10. PHARMACOL. CATEGORY:

Lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption.

11. DOSAGE FORM: Solution/Nasal Spray

12. STRENGTH/POTENCY: 200 IU/spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

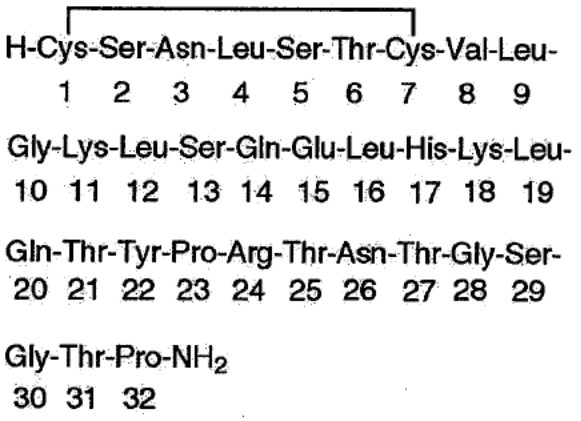
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2 [Disulfide Bridge: 1-7]

$C_{145}H_{240}N_{44}O_{48}S_2$; MW=3431.9 (*CAS 47931-89-1*)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	3/25/04	By Cai HFD-620
	III			4	N/A		
	III			4	N/A		

Chemistry Review Data Sheet

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 –Type 1 DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application; 5 – Authority to reference not granted 6 – DMF not available; 7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	--	
EES	Pending	--	
Methods Validation	Not to be issued at this cycle	--	
Labeling	Deficient	6/3/04	R. Wu
Bioequivalence/Waiver	Deficient	3/30/04	S. Pradhan
EA	N/A	--	
Radiopharmaceutical	N/A	--	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-396

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
The ANDA is not approvable pending clarification of Major chemistry issues. The firm need provide a new exhibit batch, since the API manufacture has moved into a new facility and (b) (4) (b) (4). Additional including raw material controls, API manufacturing control (DMF deficiencies), and controls of the drug product at release and stability (specifications and test methods). The Bioequivalence Studies and Labeling are pending review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug product, Calcitonin-Salmon Nasal Spray is labeled for nasal use. The drug product is packaged in 2 mL fill glass bottles with a meter pump. The pumps, following priming, will deliver 0.09 mL of solution each spray. Each bottle contains at least 14 doses. The information provided for the Nasal Pump used for this drug product is found incomplete at this time.

- There are no USP monographs for Calcitonin-Salmon (drug substance or drug product). NOVEX has developed its own in-house methods for drug product and drug substance testing. There are several issues regarding the DS/DP specifications and test methods that need to be resolved. The "Spray Pattern" specification needs to be revised to be more specific. All related DS/DP test methods will be evaluated by the FDA laboratories when all issues are solved. NOVEX's drug product manufacturing process is found acceptable.

- Based on results generated from their stability data (accelerated and long-term conditions) under the accelerated conditions, this drug product has been found very stable. No significant trends for assay drop (or increase) were found. No significant trends of increase for each individual related peptide or total related

peptides were found. The available stability data support a 24 months expiration dating period.

- The [redacted](b) (4) is supplied by [redacted](b) (4) (DMF [redacted](b) (4)). DMF [redacted](b) (4) was reviewed and a deficiency letter will be issued to the DMF holder. NOVEX's [redacted](b) (4) specifications are found not acceptable at this time.

B. Description of How the Drug Product is Intended to be Used

- The recommended dose for Calcitonin-Salmon Nasal Spray is one spray per day.
- Stored unopened bottles in refrigerator between 36-46 ^{0}F (2-8 ^{0}C). protect from freezing. Stored opened bottles at RT in an upright position for up to 30 days. Discard all unrefrigerated bottles after 30 days.
- The expiration for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

MAJOR Chemistry Issue: [redacted](b) (4)

MINOR Chemistry Issues:

- Controls for DS/DP
- API manufacturing (DMF)

Bio deficiencies
Labeling deficiencies
Pending Method Validation
Pending EES

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

Executive Summary Section

B. Endorsement Block

HFD-620/B.Cai,Ph.D/4/19/04 7/19/04
HFD-620/S.Liu,PhD/ S.H. Liu 7/20/04
HFD-620/W.Pamphile, PM/ 7/20/04
V:\FIRMSNZ\NOVEX\LTRS&REV\76396cr2.doc
F/T by:

C. CC Block

ANDA 76-396
ANDA DUP
DIV FILE
Field Copy

Following this page, 22 pages withheld in full (b)(4)-CCI-TS

NOVEX provided a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approve prior to its completion.

32. **LABELING** Deficient by R. Wu on 6/3/04

Items Reviewed by Chemist: Satisfactory per CR#1

33. **ESTABLISHMENT INSPECTION** Pending

34. **BIOEQUIVALENCE** Deficient by S. Pradhan on 3/30/04

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

Satisfactory pr CR#1.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-396 APPLICANT: NOVEX Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/Spray

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please respond to the bioequivalence deficiencies faxed on March 30, 2004.

2. Please respond to the labeling deficiencies faxed on June 3, 2004.

3. Please provide any stability data on the new exhibit batch that may be available.

Sincerely yours,

for 7/20/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-396
ANDA DUP 76-396
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/B. Cai, Ph.D/03/31/04, 04/19/04
HFD-627/S.Liu,PhD/ S. H. Liu 7/20/04
HFD-617/W.Pamphile, PM 7/20/04
V:\FIRMSNZ\NOVEX\LTRS&REV\76396CR2.DOC
F/T by:

TYPE OF LETTER: NOT APPROVABLE - Major

ANDA 76-396

Calcitonin-Salmon Nasal Spray, 200 IU/Spray
(2 mL fill volume and 3.7 mL fill volume)

Apotex Inc.
(Formerly Novex Pharma)

Bing Cai, Ph. D.

Division of Chemistry I
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-396

2. REVIEW #: 3 (Revised)

3. REVIEW DATE: June 7, 2005; September 7, 2007, Dec. 10, 2007

4. REVIEWER: Bing Cai, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NOVEX	
Original Submission	08-Apr-2002
Amendment/CMC	23-Sep-2002, 11-Feb-2004, 25-Feb-2004
Bio Amendment	29-Jul-2004, 13-Aug-2004, 18-Aug-2005, 02-Sep-2005, 05-Apr-2006
Labeling Amendment	23-April-2003, 29-Jul-2004, 18-May-2005, 23-FEB-2006
FDA	
Refuse to Filling	11-Jun-2002
Acceptable for Filling as 17-Jul-2002	16-Sep-2002
CMC CR#1/NA letter	03-Jan-2003
CMC CR#2/NA letter	29-July-2004
T-Con	09-Feb-2007, 02-Mar-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC/Major Amendment	1/31/2005
CMC/Gratuitous Amendment	4/19/2005
Amendment/CMC	2/20/2007
Amendment/CMC	7/23/2007
Amendment/CMC	11/09/2007
Amendment/CMC	11/28/2007
Amendment/CMC	04/30/2008
Amendment/CMC/USP<467>	7/18/08 & 7/22/08

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc. (Formerly Novex Pharma)
Address:	380 Elgin Mills Road East Richmond Hill, Ontario, Canada L4C 5H2
Representative:	Bernice Tao
Telephone FAX:	905-884-7412 ext 2445 / (905) 884-2050 905-884-9876

US Agent:	Apotex Corp.
Address:	2400 North Commerce Parkway, Suite 400 Weston, Florida 33326
Representative:	Kiran Krishnan
Telephone: Fax:	954-384-3986 954-349-4233

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Calcitonin-Salmon Nasal Spray

9. LEGAL BASIS FOR SUBMISSION: 505(j)(2)(A)(vii)(**IV**)

The original submitted Paragraph III Certification is revised to a Paragraph IV Certification in an amendment dated September 25, 2002.

Reference Product: Miacalcin® Nasal Spray
Manufacturer: Novartis (NDA 20-313)

10. PHARMACOL. CATEGORY:

Lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption.

11. DOSAGE FORM: Solution/Nasal Spray

12. STRENGTH/POTENCY: 200 IU/Spray

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2 [Disulfide Bridge: 1-7]

$C_{145}H_{240}N_{44}O_{48}S_2$; MW=3431.9 (*CAS 47931-89-1*)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
1 2 3 4 5 6 7 8 9

Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-
10 11 12 13 14 15 16 17 18 19

Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
20 21 22 23 24 25 26 27 28 29

Gly-Thr-Pro-NH_2
30 31 32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	9/9/07	By Cai HFD-620
	III			4	N/A		
	III			4	N/A		

* No new amendments as o July 21, 2008

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 –Type I DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application; 5 – Authority to reference not granted
6 – DMF not available; 7 – Other (explain under "Comments")

[2] Action code for DMF Table: Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	--	
EES	Satisfactory	20-12-07	S. Adams
Methods Validation	Issued in this cycle*	--	
Labeling	Satisfactory	3/9/2006	R. Wu
Bioequivalence/Waiver	Satisfactory	05/17/06	S. Pradhan
EA	N/A	--	
Radiopharmaceutical	N/A	--	

*The applicant has provided a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-396

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The ANDA is approvable, pending CP (2005P-0360).

The MVP is issued in this cycle.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug product, Calcitonin-Salmon Nasal Spray, is labeled for nasal use. The drug product is packaged as 2 mL and 3.7 mL fill in glass bottles with a meter pump. The pumps, following priming, will deliver 0.09 mL of solution each spray. Each bottle contains at least 14 and 30 doses respectively. The information provided for the Nasal Pump used for this drug product is found satisfactory.

- There is USP monograph for Calcitonin-Salmon drug substance or drug product. In the amendment dated 4/30/2008, the applicant has revised both DS/DP specifications to meet the USP monographs. The applicant has developed the in-house methods for drug product and drug substance testing. All issues regarding the DS and DP specifications and test methods are resolved. The applicant's drug product manufacturing process is found acceptable.

- Based on the accelerated stability data generated from their new stability batches, the drug product has been found very stable (b) (4) (b) (4). No significant trend for assay drop (or increase) is found. No significant trend for increase of each individual related peptide or total related peptides is also found. The available stability data support a tentative 24 months expiration dating period at 5 deg C (refrigerated conditions).

- The (b) (4) is supplied by (b) (4) (DMF (b) (4)). DMF (b) (4) was reviewed and found adequate. The applicant's drug substance specifications are found acceptable at this time.

B. Description of How the Drug Product is Intended to be Used

- The recommended dose for Calcitonin-Salmon Nasal Spray is one spray per day.
- Store unopened bottles in refrigerator between 36-46 ^{0}F (2-8 ^{0}C). Protect from freezing. Store opened bottles at RT in an upright position for up to 30 days. Discard all unrefrigerated bottles after 30 days.
- The expiration for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

Following this page, 29 pages withheld in full (b)(4)- CCI/TS

The applicant has provided a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approve prior to its completion.

32. **LABELING** Acceptable by R. Wu, 3/9/06.

33. **ESTABLISHMENT INSPECTION** Acceptable.

34. **BIOEQUIVALENCE** Satisfactory, MQ, 5-17-07.

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** Satisfactory pr CR#1.

cc: ANDA 76-396
ANDA DUP 76-396
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Cai, Ph.D./06/27/05, 09/11/07, 10/30/07, 07/18/08, July 21, 2008
HFD-620/Raj Bykadi, Ph.D./ October 2, 2007/Dec 21, 2007/Dec 26, 2007/ July 21, 2008
HFD-617/Ben Danso, Pharm. D./ 1-15-08;7-22-08

V:\CHEMISTRY DIVISION I\TEAM 5\FINAL VERSION FOR DFS (ORIGINAL)\76396CR3A.DOC

TYPE OF LETTER: CMC APPROVABLE

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

/s/

Bing Cai
8/27/2008 04:43:05 PM
CHEMIST

Gururaj Bykadi
8/28/2008 05:46:06 AM
CHEMIST

Benjamin Danso
9/3/2008 09:02:36 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

BIOEQUIVALENCE REVIEWS

DEC 2 2003

Calcitonin-salmon
Nasal Spray, 200 IU/spray
ANDA # ***76-396***
Reviewer: Sikta Pardhan
V:\Firmsnz\Novex\ltrs&rev\76396N0402

Novex Pharma
Richmond Hill
Ontario, Canada
Submission Date:
April 5, 2002
September 11, 2002
June 5, 2003

REVIEW OF IN VITRO BIOEQUIVALENCE STUDY DATA

Executive Summary

Novex Pharma has conducted the in vitro bioequivalence study on its Calcitonin-salmon Nasal Spray, 200 IU/spray comparing it with the reference listed drug (RLD), Miacalcin^R Nasal Spray, 200 IU/spray, manufactured by Novartis. Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance issurd on April 3, 2003, the in vitro bioequivalence studies were conducted on the following testing: The Unit Dose, Droplet Size Distribution (laser diffraction and cascade impaction), Spray Pattern, and Plume Geometry. However, the in vitro study conducted on the test product has been found incomplete due to the deficiencies in the spray pattern, in cascade impaction and in plume geometry testing.

Submission Summary

The firm has submitted an application (dated April 5, 2002) for its Calcitonin-salmon Nasal Spray, 200 IU/spray and requested a waiver of *in vivo* bioequivalency testing requirements under 21 CFR 320.22 (b)(3). The firm has provided additional information on the formulation in two amendments (dated September 11, 2002 and June 5, 2003).

Background

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals. Calcitonin-salmon is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. The reference listed drug (RLD) is Miacalcin^R Nasal Spray, 200 IU/spray (200 IU per 0.09 mL actuation), manufactured by Novartis.

Calcitonin-salmon Nasal Spray is provided in 2x2 ml glass bottles (individual box containing two glass bottles with attached pumps (NDC 60505-0823-0) as a solution for nasal administration. The recommended dose for Calcitonin-salmon Nasal Spray 200 IU/spray is one spray per day. Each bottle contains 2200 IU/mL calcitonin- salmon, sufficient medication for at least 14 doses.

Calcitonin- salmon Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in female greater than 5 years post-menopause with low bone mass relative to healthy pre-menopausal females.

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.

Formulation:

The firm has provided comparative formulation data of its proposed test product and Miacalcin[R] Nasal Spray, 200 IU/spray manufactured by Novartis (see ***Table 1*** below) in the original submission dated April 5, 2002.

TABLE 1. FORMULATION COMPARISON

Composition	Reference Miacalcin[R] Nasal Spray 200 IU/spray		Test Calcitonin-Salmon Nasal Spray 200 IU/spray	
	Qualitative[2]	Quantitative (g/L)	Qualitative	Quantitative (g/L)
Active	Calcitonin (Salmon)	2200000IU/L[1]	Calcitonin (Salmon) EP	2200000IU/L
Inactive	Benzalkonium Chloride	(b) (4)	Benzalkonium Chloride Solution NF/EP (b) (4)	(b) (4)
	Hydrochloric Acid	To adjust pH to (b) (4)	Hydrochloric Acid NF/EP	q.s. to adjust pH (b) (4)
				(b) (4)
				(b) (4)
	Purified Water	Present	Purified Water NF/EP	(b) (4)
	Sodium Chloride	(b) (4)	Sodium Chloride USP/EP	

[1] As per label claim

[2] Qualitative ingredient summary and amount of inactive drug substance for the Novartis product are based on the most current carton labeling.

Two issues were raised by the Agency on the sponsor's formulation:

- (a) (b) (4) and
- (b) lack of unit of Benzalkonium Chloride solution used
- As per the request of the FDA, Novex Pharma has promised to update the formulation of the test product (***amendment dated September 11, 2002***). The firm has stated

that [redacted] was never used in the submitted batch (for in vitro studies), Lot No. 1X200. A revised composition statement is presented ***TABLE 1A*** below:

TABLE 1A

	Calcitonin-Salmon Nasal Spray, 200 IU/spray					
Ingredient	Per Dose (Theore-tical) 0.09 mL	Per Unit (Theoretical) 2 mL	Per ANDA Batch [redacted]	Per Production batch [redacted] (Theore-tical)	Per Production batch [redacted] (Theore-tical)	Per Production batch [redacted] (Theore-tical)
Active: Calcitonin (Salmon) EP*	200 IU	4400IU	[redacted]			
Inactive: Benzalkonium Chloride Solution NF/EP [redacted]	[redacted]					
Purified Water USP/ES	q.s.	q.s.	q.s.	q.s	q.s.	q.s.
Hydrochloric Acid NF/EP	Adjust pH to	Adjust pH to	[redacted]	Adjust pH to	Adjust pH to	Adjust pH to [redacted]
Sodium Chloride USP/EP	[redacted]					

*Quantity to be added based on "as is" potency.
** Quantity to be added based on assay and density values.

Novex Pharma has further committed to revise the following documents to reflect the removal of [redacted] from the Calcitonin-Salmon Nasal Spray, 200 IU/spray formulation:
A. Master Formula [redacted]; B. Product Labeling; C. Stability Protocol

- As per the request of the Division of Bioequivalence, Novex Pharma has updated the formulation (presented below in TABLE 1B) of the test product and included units (g) for Benzalkonium Chloride Solution NF/EP [redacted] in the ***amendment dated June 5, 2003***.

TABLE 1B.

Composition	Reference Miacalcin^{R} Nasal Spray 200 IU/spray		Test Calcitonin-Salmon Nasal Spray 200 IU/spray	
	Qualitative[2]	Quantitative (g/L)	Qualitative	Quantitative (g/L)
Active	Calcitonin (Salmon)	2200000IU/L[1]	Calcitonin (Salmon) EP	2200000IU/L
Inactive	Benzalkonium Chloride	[redacted]	Benzalkonium Chloride Solution NF/EP [redacted]	[redacted]
	Hydrochloric Acid	To adjust pH to [redacted]	Hydrochloric Acid NF/EP	q.s. to adjust pH to [redacted]
			[redacted]	
	[redacted]			
	Purified Water	Present	Purified Water NF/EP	
	Sodium Chloride	[redacted]	Sodium Chloride USP/EP	

[1] As per label claim

[2] Qualitative ingredient summary and amount of inactive drug substance for the Novartis product are based on the most current carton labeling.

(b) (4)

Comments:

1. The firm has informed the FDA that (b) (4) was never used in the submitted batch (for in vitro studies), Lot No. 1X200.

2. Hence, the composition of the test product is quantitatively and qualitatively the same as that of the reference product. The CMC review also indicates that the test product is Q1/Q2 to the innovator's formulation based on the information from NDA 20-313/S-18.

Drug Products:

Reference Product: The in vitro bioequivalence studies were performed on three lots of the reference product, Miacalcin[R] Lot Nos. 477D9264, 479D9655 and 486E9658.

Test Product: The vitro study was conducted on one lot of the test product (Novex Pharma Lot No. 1x200) packaged with three different lots of the nasal spray pumps in the following quantities: Novex Pharma QC No. 6356 (b) (4), QC No. 6357 (b) (4), QC No. 6358 (b) (4).

Procedures and Information Applicable to All Tests:

The pumps used in both cases of the test and reference products were obtained from (b) (4). The supplier of actuator used in both cases was also (b) (4). Since it was not possible to obtain further information regarding the Innovator's metering device due to confidentiality reasons, Novex Pharma performed a physical comparison of its metering device with that of the Innovator's, and the resultant data have been presented in Table No. VI-20, p-484, Vol.1.2. These data indicates that corresponding pump components have the same identities, both in the IR spectra and melting point peak temperatures. A copy of Novex Pharma's pump drawing (Figure VI-22) is attached.

All actuations of the nasal spray products were done using an automated actuator system manufactured by (b) (4) to actuate the nasal sprays in a reproducible manner. The actuator's operating conditions are presented below:

Parameters	[redacted] Pump
Dose Time (msec)	20 ± 2
Return Time (msec)	30 ± 5
Hold Time (sec)	0.5
Actuation Force (kg)	6.0±0.5

Sponsor has used [redacted] Pump of volume, [redacted] mL (Figure VI-22) as presented on page 18.

In Vitro Bioequivalence tests

Consistent with the recommendations made in the revised draft guidance on BA/BE studies for nasal aerosols and nasal sprays issued on April 3, 2003, the in vitro bioequivalence studies were conducted on the following testing: the unit dose, priming and re-priming, droplet size distribution (laser diffraction and cascade impaction), spray pattern, and plume geometry.

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested. The amount of drug per spray was determined by a validated High Performance Liquid Chromatographic (HPLC) method (LOQ=3.98 µg/mL). The method was appropriately validated with respect to specificity, linearity, accuracy, and precision.

Priming:

The number of sprays required to prime the pump was determined by assaying the first seven sprays of each unit. The results indicate that the Novex product is fully primed after 4 actuations but the reference product needs 5 actuations to produce a spray content close to 100% of the label claim.

Re-Priming:

According to the Miacalcin^{R} Patient Information Insert (labeling), the medication is administered daily without having to re-prime the pump. A re-priming study was performed by leaving the bottle for a 24-hour period of non-use in both the vertical and horizontal positions. The sponsor's results indicate that the pumps do not lose their prime (see Tables attached on page Nos. 19 & 20).

Single Actuation Content (Spray Content Uniformity) through Container Life:
Assay results from Spray Nos. 5 to 18 constitute dose uniformity through container life. The sponsor has provided data (see Table No. VI-5, p309, Vol.1.1) from individual sprays at the beginning and end of container life. Table 2 presents a summary of all units tested based on calculation performed in the Division of Bioequivalence.

Table 2. Unit Dose (Unit Spray Content) Data

		Mean		Variability (%CV)			Test/Ref		P-value
Prod	Sec.	Arith.	Geo	Within-lot (N=10)	Bet-lot (N=3)	Total N=30	Arith. (N=30)	Geo N=30)	
TEST	BEG	96.9	96.80	4.0	0.5	3.38	1.08	1.08	0.000
	END	98.7	98.65	2.0	1.6	4.12	0.98	0.98	0.1073
REF	BEG	89.6	89.51	5.4	1.6	5.32			
	END	100.8	100.7	3.2	2.9	4.12			

Beg=Spray#5
End=Spray#18

The data was obtained with the bottle in the vertical position. In order to determine if the spray content was affected by the orientation of the bottle during spray collection, spray content uniformity test was also performed with the bottle tilted at a 45^0 angle to mimic actual patient use. Results showed no difference in quantity per spray between the test and reference products.

Comments on the Single Actuation Content Data

1. For Novex Pharma's Calcitonin-salmon, the geometric mean values at actuations #5 and #18 are similar to the corresponding reference product values. The test product exhibited similar variability (%CV) as the reference product with regard to the unit dose data.

2. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

3. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products. The Single Actuation Content data were also analyzed by the Population Bioequivalence Methodology stated in the June 1999 draft Nasal BA/BE Guidance. The Sigma and Epsilon values used in these analyses were 0.1

and 0.01, respectively. The results of these analyses also support equivalence of the test and reference products with regard to the single actuation content.

Priming Tail Off Comment:

Based on the April 2003 revised draft nasal BA/BE guidance, Priming Tail Off data are not required, if the test product demonstrates equivalence at the labeled first (beginning) and last (end) primed actuation. The data given above demonstrate that the test product delivers the same amount of drug per actuation at the beginning and end of product use life.

Spray Pattern:

Spray pattern provides information about the shape and density of the plume following actuation. The spray pattern determination was performed with the (b) (4) laser-based spray characterization and visualization system.

Spray patterns were determined on single actuations at 3 cm, 4 cm and 5 cm from the actuator to the target at the beginning and end of bottle life. Minimum diameter (D_{min}), maximum diameter (D_{max}), and the ovality ratio (D_{max}/D_{min}) of spray patterns were analyzed for each of the three distances. These parameters were based on the actual pattern shape (secondary analysis) using the "Auto Spray Pattern Tool", which automatically determine the Dmax and Dmim axes.

The firm has also quantitated spray patterns by the "Ellipse fitting "method. However the Agency does not accept the "Ellipse fitting" method.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table 3. These data are based on the actual spray pattern analysis and not quantitated by the "Ellipse fitting "method.

Table 3. Spray Pattern (Test Product) and Test/Ref Ratios

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Geo	p
		3	Dmax	45.38	44.64	11.9-21.9	7.98	19.09	1.22	0.00000
		3	Dmin	33.34	32.79	15.2-21.8	1.63	18.15	1.22	0.00002
		3	Oval. Ratio	1.37	1.36	6.3-16.3	7.01	12.47	1.03	0.27491
		4	Dmax	58.94	57.99	14.1-19.2	9.29	18.23	1.29	0.00000
	BEG	4	Dmin	40.93	40.12	16.8-22.6	2.16	19.33	1.22	0.00004
		4	Oval. Ratio	1.46	1.45	7.0-14.9	8.30	12.55	1.07	0.03955
		5	Dmax	75.91	74.37	14.1-23.8	2.08	20.23	1.27	0.00000
		5	Dmin	50.48	49.16	19.0-26.8	5.36	22.47	1.23	0.00020
TEST		5	Oval. Ratio	1.53	1.51	7.7-17.2	7.17	13.50	1.03	0.27620
		3	Dmax	42.55	42.00	11.7-20.8	6.14	16.44	1.21	0.00000
		3	Dmin	31.68	31.19	15.0-20.7	1.60	18.05	1.21	0.00003
		3	Oval. Ratio	1.35	1.35	5.8-12.5	7.02	10.90	1.01	0.86679
		4	Dmax	57.85	56.45	18.2-27.0	6.63	22.83	1.29	0.00000
	END	4	Dmin	40.38	39.11	19.2-31.0	2.91	26.31	1.25	0.00017
		4	Oval. Ratio	1.46	1.44	7.0-19.5	6.80	15.52	1.03	0.30941
		5	Dmax	71.95	70.79	12.4-22.4	6.15	17.63	1.29	0.00000
		5	Dmin	46.59	45.37	18.1-26.6	1.48	22.48	1.22	0.00012
		5	Oval. Ratio	1.58	1.56	5.4-20.9	8.88	16.87	1.06	0.09237

Spray Pattern - (REF Product)

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Variability (%CV) Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
		3	Dmax	35.66	35.51	7.2-10.1	4.65	9.51
		3	Dmin	27.03	26.88	6.7-13.2	6.22	11.19
		3	Oval. Ratio	1.33	1.32	7.7-9.5	2.97	8.52
		4	Dmax	45.20	44.97	8.2-12.2	3.83	10.44
	BEG	4	Dmin	33.19	32.98	7.9-14.4	5.61	11.50
		4	Oval. Ratio	1.37	1.36	7.9-8.8	2.49	8.39
		5	Dmax	59.01	58.61	10.2-12.9	5.47	11.87
		5	Dmin	40.29	39.96	8.3-15.2	7.13	12.89
REF		5	Oval. Ratio	1.47	1.47	8.8-12.4	1.96	10.24
		3	Dmax	34.87	34.72	8.6-10.4	3.06	9.45
		3	Dmin	25.94	25.83	7.5-10.6	4.23	9.60
		3	Oval. Ratio	1.35	1.34	6.2-8.2	1.88	7.34
		4	Dmax	43.89	43.73	8.1-9.1	3.34	8.69
	END	4	Dmin	31.36	31.18	9.7-10.6	6.05	10.97
		4	Oval. Ratio	1.41	1.40	8.7-9.5	3.02	9.07
		5	Dmax	55.03	54.71	6.5-12.7	4.44	11.03
		5	Dmin	37.49	37.23	6.1-14.1	7.38	11.82
		5	Oval. Ratio	1.48	1.47	10.2-13.8	2.80	11.93

Comments on Spray Pattern Analysis:

1. The ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90-1.11 range.

2. However, the ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was not within the acceptable 0.90-1.11 at both life sectors.

3. The overall variability of the test product was more than that of the reference product.

4. Based on the above data, the Spray Pattern data are not acceptable. These data were also analyzed in the DBE using the Population Bioequivalence method (as outlined in the June 1999 draft Nasal BA/BE guidance). The results of these analyses also demonstrate the lack of equivalence in Spray Patterns between the test and reference products.

5. The firm should note that based on the April 2003 draft Nasal BA/BE Guidance, measures of Spray pattern, using automated Laser analyses, are Area and Ovality ratio. Measurement of Dmax and Dmin axes is not required for such analyses. The firm has the option of repeating Spray Pattern Testing using the conventional impaction technique (thin layer chromatography). If this technique is used, the Agency encourages the firm to use computerized image measurements to minimize potential bias.

Droplet size distribution

a. Laser Diffraction:

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. However, based on the revised draft Nasal BA/BE guidance, bioequivalence evaluation is based only on data of beginning and end sectors of unit life.

At each sector of unit life, each unit was actuated at three distances (3 cm, 5 cm, and 8 cm) relative to the (b) (4) laser beam. At each distance, measurements were taken at three delay times. The three delay times characterize three regions in the plume life based on % transmission:

Plume Region	Transmission Characteristic
Plume formation (Initial)	Drops
Fully formed plume (Intermediate)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling points on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distances. The firm submitted D10, D50, D90 and SPAN data. Based on the revised draft Nasal BA/BE guidance, bioequivalence evaluation is based only on D50 and SPAN data for the fully formed plume (Intermediate). A summary of these data based on the reviewer's calculations is given in Table 4 & 5.

Table 4. Droplet Size Distribution - D50 Data (Test and Ref. Products) and Test/Ref

PROD. TEST	Stage	Distance	Plume Formation	Mean Arith (N=30)	Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-Lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Geo.	P
		3		31.31	31.24	5.5-8.5	2.24	6.869	0.96	0.04892
	BEG	5	Intermediate	34.72	34.69	3.5-4.4	2.61	4.422	0.99	0.68935
		8		42.45	42.38	4.8-7.7	1.43	5.87	1.017	0.23687
		3		31.58	31.51	4.9-8.6	2.55	7.01	0.96	0.03733
	MIDDLE	5	Intermediate	35.55	35.51	2.3-5.3	2.25	4.42	1.04	0.12534
		8		42.71	42.64	4.6-6.6	2.29	5.68	1.02	0.05582
		3		32.15	32.07	6.3-8	2.14	7.19	0.97	07132
	END	5	Intermediate	35.58	35.53	2.8-6.0	2.15	5.13	1.00	0.67868
		8		43.63	43.59	3.2-5.1	1.82	4.53	1.03	01078
REF.										
		3		32.45	32.38	5.5-7.7	3.61	7.06		
	BEG	5	Intermediate	34.89	34.86	1.7-5.0	0.89	3.81		
		8		41.73	41.68	2.7-5.6	0.45	4.39		
		3		32.69	32.62	5.3-6.8	1.3	6.10		
	MIDDLE	5	Intermediate	34.97	34.95	3.1-4.8	0.56	3.93		
		8		41.74	41.70	2.9-5.6	0.66	4.29		
		3		33.19	33.12	3.9-8.3	0.66	4.29		
	END	5	Intermediate	35.43	35.39	3.6-5.5	1.36	6.37		
		8		42.29	42.24	4.1-6.8	0.64	4.67		

Table 5. Droplet Size Distribution - SPAN Data (Test and Ref. Products) and Test/Ref Ratios

PROD. TEST	Stage	Distance	Plume Formation	Mean Arith (N=30)	Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-Lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Geo	P
		3		1.75	1.74	6.9-12.2	2.58	9.44	0.97	0.23266
	BEG	5	Intermediate	1.27	1.26	8.1-12.7	0.79	9.95	0.92	0.00305
		8		1.08	1.08	3.7-5.3	1.42	4.78	0.97	0.04273
		3		1.74	1.73	5.7-14.6	4.34	10.78	0.96	0.11978
	MIDDLE	5	Intermediate	1.25	1.25	6.3-8.7	2.01	7.56	0.93	0.00067
		8		1.06	1.05	5.3-8.6	2.19	6.79	0.94	0.00165
		3		1.70	1.69	4.9-8.5	0.34	7.21	0.94	0.00667
	END	5	Intermediate	1.26	1.25	7.2-12.1	2.1	9.32	0.92	0.00048
		8		1.05	1.04	5.6-13.5	2.4	9.25	0.96	0.02578
REF.										
		3		1.79	1.79	3.0-7.8	1.3	6.32		
	BEG	5	Intermediate	1.37	1.37	7.2-10.0	2.99	8.51		
		8		1.11	1.11	4.1-6.6	1.04	5.51		
		3		1.80	1.80	4.0-6.6	1.6	5.13		
	MIDDLE	5	Intermediate	1.35	1.35	3.9-7.2	2.99	8.08		
		8		1.11	1.11	5.5-7.2	1.04	5.62		
		3		1.81	1.80	5.5-11.5	2.1	8.12		
	END	5	Intermediate	1.37	1.37	6.0-9.0	2.56	7.30		
		8		1.09	1.09	5.0-8.1	1.4	6.50		

Comments on Droplet Size Distribution

1. Evaluation of the comparative droplet size distributions by laser diffraction is based on data pertaining to the fully formed plume, which is represented by the intermediate plume stage. Based on the geometric mean data for the intermediate portion of the plume, the T/R ratios for D50 and SPAN are within the 0.9-1.11 range, used hitherto by DBE for acceptance of solution nasal spray products.

2. For D50 and SPAN, the variability for the test product is comparable to that of the reference product in majority of the cases.

3. The droplet size distribution data were also analyzed in the DBE using the Population Bioequivalence method stated above. Based on this analysis the test product's D50 and Span are equivalent to those of the reference product.

b. Cascade Impaction:

The firm has indicated that Cascade impaction performed on the beginning and end use of the product has been done by grouping the analysis of drugs deposited on various stages on the impactor as instructed by the Agency. However, the firm did not provide any detailed methodology.

Comment on Cascade Impaction Data:

1. The data showed no drug deposition below the top stage of the cascade impactor. In the Agency's experience with the aqueous nasal sprays, low but measurable levels of drug are observed below the top stage of the impactor. The factors, which may improve deposition in the lower stage include (1) development and use of an assay with greater sensitivity and (2) the use of an atomizing chamber different from the USP throat (used by the firm) recommended for oral inhalation products. The revised draft Nasal BA/BE guidance issued on April 2003 recommends the use of a 2L or larger flask. Hence, the firm should be requested to repeat the test following the recommendations made in the guidance.

2. The firm should be requested to provide the detailed methodology of Cascade impaction (test, including the operating parameters).

Plume Geometry Data:

The intent of the plume geometry test procedure was to provide the means by which a visual record of the features of an aerosol cloud (plume) can be used to demonstrate the comparability or potential differences between the test and reference products.

Plume geometry was studied using the (b) (4) Measurements were done for plume angle, plume width and plume height. Based on the advice received from DBE, the firm measured plume height and width only at the plume initiation phase. However, plume angle was measured for all three plume phases (i.e. initiation, formation and dissipation). Plume angle, plume height and plume width, were determined for images taken at two orientations, 0 degree and 90 degree. The following table represents a summary of plume geometry data based on the reviewer's calculations.

TABLE 6.

0-Degree View

	TEST					REF				
	Plume Angle			Plume	Plume	Plume Angle			Plume	Plume
	Initial	Formation	Dissipation	Height	Width	Initial	Formation	Dissipation	Height	Width
Within-lot	6.74	3.19	5.50	3.34	7.82	5.01	3.20	5.45	2.68	6.04
%CV	6.27	3.13	3.67	6.36	8.02	5.69	3.57	6.12	5.33	12.15
	7.97	5.50	3.35	3.78	9.86	7.11	2.55	6.50	4.77	12.80
Bet.-lot %CV	2.80	1.25	2.02	2.53	5.76	0.90	0.87	0.96	2.08	1.91
Total										
Mean	81.45	86.74	65.16	68.65	27.88	81.28	88.70	65.43	66.82	26.96
%CV	7.14	4.07	4.49	4.95	9.53	5.84	3.10	5.89	4.56	10.45
Geomean	81.24	86.67	65.10	68.57	27.76	81.14	88.66	65.33	66.75	26.81
T/R										
Mean	1.00	0.98	1.00	1.03	1.03					
Goemean	1.00	0.98	1.00	1.03	1.04					
p-value	*0.914*	*0.033*	*0.761*	*0.054*	*0.257*					

90-Degree View

	TEST					REF				
	Plume Angle			Plume	Plume	Plume Angle			Plume	Plume
	Initial	Formation	Dissipation	Height	Width	Initial	Formation	Dissipation	Height	Width
Within-lot	9.53	4.83	2.82	2.24	9.13	5.05	3.70	4.88	3.90	12.06
%CV	10.67	1.88	6.07	4.15	8.88	7.26	4.23	4.72	5.03	7.29
	6.03	0.86	2.74	2.20	7.13	5.95	4.59	5.29	4.73	10.94
Bet.- Lot %CV	1.30	1.55	1.64	1.03	3.17	0.91	0.70	1.59	1.24	2.51
Total										
Mean	80.87	86.37	64.29	69.02	28.57	79.39	87.73	64.46	67.65	26.79
%CV	8.72	3.16	4.29	3.03	8.56	6.00	4.08	4.98	4.53	10.19
Geomean	80.56	86.33	64.23	68.99	28.46	79.25	87.66	64.39	67.58	26.66
T/R										
Mean	1.02	0.98	1.00	1.02	1.07					
Goemean	1.02	0.98	1.00	1.02	1.07					
p-value	*0.42*	*0.10*	*0.84*	*0.03*	*0.02*					

Comments on Plume Geometry Data:

1. SOP for Plume Geometry measurements should be provided.

2. The test/ref ratios of the geometric means for plume angles are within the acceptable limits of 0.9 - 1.11.

3. It is noted, however, the width measurements are not acceptable, because they do not appear to represent the observed width of the plume. Furthermore, it not clear if all measurement were made at the same distance from the orifice.

4. Based on the submitted data, the T/R ratio of geometric means of spray width (based on plume geometry) were in the range of 1.03-1.07. These data suggest that the width of the test product spray is similar to that of the reference product.

   On the other hand, T/R ratios for Dmax (based on spray pattern) were in the range of 1.22 - 1.29, which indicates that the width of the test product product spray pattern is considerably greater than that of the reference product. The firm should explain these results, given that the same technique ((b) (4)) was used for both plume geometry and spray pattern analyses.

5. To impart objectivity to the width measurements, the width should be measured at a fixed distance from the actuator orifice. As recommended in April 2003 draft Nasal BA/BE guidance, it is requested that the width should be measured at the greatest distance chosen for the spray pattern analysis (5 cm for the present study). Plume geometry SOP should provide details methodology, including the criteria employed for defining the limits of the spray width.

OVERALL DEFICIENCY:

1. For Spray Pattern Analysis, the ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90-1.11 range. However, the ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was not within the acceptable 0.90-1.11 at both life sectors. The overall variability of the test product was more than that of the reference product. Hence, the Spray Pattern data are not acceptable. These data were also analyzed in the DBE using the Population Bioequivalence method (as outlined in the June 1999 draft Nasal BA/BE guidance). The results of these analyses also demonstrate the lack of equivalence between the test and reference products' Spray Patterns. The firm should note that based on the April 2003 draft Nasal BA/BE Guidance, measures of Spray pattern, using automated Laser analyses, are Area and Ovality ratio.

Measurement of Dmax and Dmin axes is not required for such analyses. The firm has the option of repeating Spray Pattern Testing using the conventional impaction technique (thin layer chromatography). If this technique is used, the Agency encourages the firm to use computerized image measurements to minimize potential bias.

2. In the cascade impactor study, the data showed no drug deposition below the top stage of the cascade impactor. In the Agency's experience with the aqueous nasal sprays, low but measurable levels of drug are observed below the top stage of the impactor. The factors, which may improve deposition in the lower stage include (1) development and use of an assay with greater sensitivity and (2) the use of an atomizing chamber different from the USP throat (used by the firm) recommended for oral inhalation products. The revised draft Nasal BA/BE guidance issued on April 2003 recommends the use of a 2L or larger flask. Hence, the firm should be requested to repeat the test considering the recommendations made in the guidance. The firm should be requested to provide the detailed methodology of Cascade impaction (test, including the operating parameters).

3. The *in vitro* testing conducted on plume geometry is deficient. SOP for Plume Geometry measurements should be provided. The test/ref ratios of the geometric means for plume angles are within the acceptable limits of 0.9 - 1.11. However, the width measurements are not acceptable, because they do not appear to represent the observed width of the plume. Furthermore, it not clear if all measurement were made at the same distance from the orifice.

   Based on the submitted data, the T/R ratio of geometric means of spray width (based on plume geometry) were in the range of 1.03-1.07. These data suggest that the width of the test product spray is similar to that of the reference product.

   On the other hand, T/R ratios for Dmax (based on spray pattern) were in the range of 1.22 - 1.29, which indicates that the width of the test product product spray pattern is considerably greater than that of the reference product. The firm should explain these results, given that the same technique ((b) (4)) was used for both plume geometry and spray pattern analyses.

   To impart objectivity to the width measurements, the width should be measured at a fixed distance from the actuator orifice. As recommended in April 2003 draft Nasal BA/BE guidance, it is requested that the width should be measured at the greatest distance chosen for the spray pattern analysis (5 cm for the present study). Plum geometry SOP should provide details methodology, including the criteria employed for defining the limits of the spray width.

RECOMMENDATION

The in vitro performance data submitted by Novex Pharma for its Calcitonin-salmon Nasal Spray, 200 IU/spray is incomplete due to the deficiencies in the spray pattern, in cascade impaction and in plume geometry testing.

Sikta Pradhan

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 12/2/2003

Concur: Barbara M Davit Date: 12/3/03
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 76-396 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

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Following this page, 1 page withheld in full (b)(4)-CCI/TS

Loss of Prime for Novex's Calcitonin Salmon Nasal Spray after Standing for 24 hours in the Horizontal and Vertical Positions

QC #	Code #	After Standing for 24 hours in Horizontal Position					
		Spray # 1		Spray # 2		Spray # 3	
		Weight (g)	Assay (%LC)	Weight (g)	Assay (%LC)	Weight (g)	Assay (%LC)
6356	7137	[redacted] (b) (4)					
	6232						
	3205						
6357	4213						
	3489						
	0751						
6358	7983						
	8311						
	8648						
Mean:		0.0915	95.11	0.0946	97.42	0.0951	96.13
CV(%):		2.0	4.2	1.7	1.9	1.6	2.4
Minimum:		[redacted] (b) (4)					
Maximum:							

QC #	Code #	After Standing for 24 hours in Vertical Position						QC #
		Spray # 1		Spray # 2		Spray # 3		
		Weight (g)	Assay (%LC)	Weight (g)	Assay (%LC)	Weight (g)	Assay (%LC)	
6356	3357 2160 3432	[redacted] (b) (4)						6356
6357	0397 4774 4324							6357
6358	5516 5922 3594							6358
Mean:		0.0921	96.14	0.0950	96.80	0.0952	98.21	Mean:
CV(%):		1.5	1.9	0.9	2.4	0.9	1.3	CV(%):
Minimum:		[redacted] (b) (4)						Minimum:
Maximum:								Maximum:

BIOEQUIVALENCY DEFICIENCIES

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. For Spray Pattern Analysis, the ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90-1.11 range. However, the ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was not within the acceptable 0.90-1.11 at both life sectors. The overall variability of the test product was more than that of the reference product. Hence, the Spray Pattern data are not acceptable. These data were analyzed in the DBE using the Population Bioequivalence method (as outlined in the June 1999 draft Nasal BA/BE guidance). The results of these analyses also demonstrate the lack of equivalence in spray patterns between the test and reference products. Please note that based on the April 2003 draft Nasal BA/BE Guidance, measures of Spray pattern, using automated Laser analyses, are Area and Ovality ratio. Measurement of Dmax and Dmin axes is not required for such analyses. You have the option of repeating Spray Pattern Testing using the conventional impaction technique (thin layer chromatography). If this technique is used, the Agency encourages you to use computerized image measurements to minimize potential bias.

2. The data showed no drug deposition below the top stage of the cascade impactor. In the FDA's experience with the aqueous nasal sprays, low but measurable levels of drug are observed below the top stage of the impactor. The factors, which may improve deposition in the lower stage include (1) development and use of an assay with greater sensitivity and (2) the use of an atomizing chamber different from the USP throat recommended for oral inhalation products. The revised draft Nasal BA/BE guidance issued on April 2003 recommends the use of a 2L or larger flask. Hence, please repeat the test considering the recommendations made in the guidance. Please provide the detailed methodology of Cascade impaction (test, including the operating parameters).

3. The *in vitro* testing conducted on plume geometry is deficient. SOP for Plume Geometry measurements should be provided. The test/ref ratios of the geometric means for plume angles are within the acceptable limits of 0.9 - 1.11. However, the width measurements are not acceptable, because they do not appear to represent the observed width of the plume. Furthermore, it not clear if all measurement were made at the same distance from the orifice.

Based on the submitted data, the T/R ratio of geometric means of spray width (based on plume geometry) were in the range of 1.03-1.07. These data suggest that the width of the test product spray is similar to that of the reference product.

On the other hand, T/R ratios for Dmax (based on spray pattern) were in the range of 1.22 - 1.29, which indicates that the width of the test product spray pattern is considerably greater than that of the reference product. Please explain these results, given that the same technique ([redacted] (b) (4)) was used for both plume geometry and spray pattern analyses.

To impart objectivity to the width measurements, the width should be measured at a fixed distance from the actuator orifice. As recommended in April 2003 draft Nasal BA/BE guidance, the width should be measured at the greatest distance chosen for the spray pattern analysis (5 cm for the present study). Plum geometry SOP should provide details methodology, including the criteria employed for defining the limits of the spray width.

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-396
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-655/ G. Singh 12-1-03
HFD-650/ Y. Huang 12/2/2003
HFD-617/ A. Sigler
HFD-650/ D. Conner 12/2/03

Printed in draft on 10-2-03
Printed in final on

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BIOEQUIVALENCE: Deficiencies

1. IN VITRO BIOEQUIVALENCY STUDIES Submission date: 04-05-02
Nasal Spray, 200 IU/spray Outcome IN

2. Study Amendment (STA) Submission date: 09-11-02
Outcome IN

3. Study Amendment (STA) Submission date: 06-05-03
Outcome IN

OUTCOME DECISIONS: ***IN*** - Incomplete

AUG 19 2005

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-396
Drug Product Name	Calcitonin-Salmon Nasal Spray,
Strength	200 IU/Spray
Applicant Name	Novex Pharma Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	
Amendment Date(s)	July 29, 2004
	January 31, 2005
Reviewer	Sikta Pradhan
First Generic	No
File Location	V:\firmsnz\Novex\ltrs&rev\76396A0704.Doc

Review of an Amendment

Executive Summary

The amendment (dated July 29, 2004) is in response to the deficiencies of the in vitro testing (plume geometry, cascade impaction and spray pattern) for the test product (2.0 mL fill volume) communicated to the firm by the Division of Bioequivalence (DBE). The firm has repeated these tests according to the Agency's recommendations. This amendment is incomplete due to the deficiency in cascade impaction testing.

In a recent amendment submitted on January 31, 2005, the firm proposed to market an additional bottle size (3.7 mL fill volume, 30 actuations). To support the proposal, the firm manufactured one batch of this new fill volume at (b) (4) (b) (4) facility, and as per the Agency's request (Sept. 24, 2004), the firm has provided data on Unit Dose (Unit Spray Content), Priming and Droplet Size Distribution on that batch. This amendment is incomplete due to the deficiency in priming.

Amendments Reviewed

I. **Amendment dated July 29, 2004.** – Response to the Agency comments (of March 30, 2004) on the test product (2.0 mL fill volume).

II. **Amendment dated January 31, 2005.** – For an additional bottle size (3.7 mL fill volume, 30 actuations).

I. Amendment dated July 29, 2004.

Agency Comment #1.

For Spray Pattern Analysis, the ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90-1.11 range. However, the ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was not within the acceptable 0.90-1.11 at both life sectors. The overall variability of the test product was more than that of the reference product. Hence, the Spray Pattern data are not acceptable. These data were analyzed in the DBE using the Population Bioequivalence method (as outlined in the June 1999 draft Nasal BA/BE guidance). The results of these analyses also demonstrate the lack of equivalence in spray patterns between the test and reference products. Please note that based on the April 2003 draft Nasal BA/BE Guidance, measures of Spray pattern, using automated Laser analyses, are Area and Ovality ratio. Measurement of Dmax and Dmin axes is not required for such analyses. You have the option of repeating Spray Pattern Testing using the conventional impaction technique (thin layer chromatography). If this technique is used, the Agency encourages you to use computerized image measurements to minimize potential bias.

Firm's response:

As per the Agency's request, the firm has repeated the spray pattern analysis using a manual (TLC) technique, TM-1628, Issue No. 2, Spray Pattern Determination for Calcitonin Salmon Nasal Spray. The resultant spray patterns were analyzed manually by the Center of Mass method as an automated instrument was not available for computerized image measurements. As per the April 2003 draft guidance, BA/BE Studies for Nasal Aerosols and Nasal Sprays for Local Action, Dmax and the Ovality ratio should be used for the statistical evaluation of BE for manual analyses. The T/R ratios for Dmax and Ovality are within the 0.9-1.11 range at distance of 3 cm and 6 cm from the actuator orifice and therefore, the firm reported, the test and reference products are equivalent in spray pattern.

Reviewer's Comment:

The firm has provided the methodology for the Spray Pattern Determination for Calcitonin Salmon nasal spray (see Attachment #3, p.1-6, Vol.4.1). In each test, three sprays of the test or reference product were actuated on to a TLC plate placed at 3 or 6 cm from the orifice. The spray pattern was visualized as a yellow color with purple background on the TLC plate after spraying with a chromogenic reagent. The true shapes of the spray patterns were outlined and Dmax and Dmin were manually determined. The firm has also provided 20% representative spray pattern images (Attachment #4, p.13-25, Vol.4.1).

The T/R ratios for Dmax, Dmin and Ovality are within the acceptable range of 99-111%. The variability of the test product is comparable to that of the reference product. Therefore, the test product is acceptable with respect to spray pattern testing.

TABLE 1
SPRAY PATTERN

	Test Product			Reference Product		
3 Cm						
	Dmax	Dmin	Oval. Ratio	Dmax	Dmin	Oval. Ratio
Within-lot (%CV)	4.05 (7.20)	3.32 (14.54)	1.24 (12.81)	3.81 (8.25)	3.34 (9.59)	1.14 (4.06)
	4.02 (10.54)	3.25 (10.28)	1.24 (10.37)	3.72 (4.16)	3.25 (7.57)	1.15 (5.64)
	4.14 (8.69)	3.36 (6.15)	1.24 (9.62)	3.69 (6.57)	3.30 (8.21)	1.12 (7.43)
Bet.-lot	4.07	3.31	1.24	3.74	3.30	1.14
%CV	1.53	1.68	0.33	1.67	1.37	1.18
Total						
Mean	4.07	3.31	1.24	3.74	3.30	1.14
%CV	8.68	10.57	4.12	6.50	8.30	5.73
Geomean	4.05	3.29	1.23	3.73	3.29	1.14
T/R						
Mean	1.09	1.00	1.09			
Goemean	1.09	1.00	1.08			
p-value	0.000386	0.877298	0.001977			

	Test Product			Reference Product		
6 Cm						
	Dmax	Dmin	Oval. Ratio	Dmax	Dmin	Oval. Ratio
Within-lot (%CV)	6.08 (6.84)	4.49 (12.88)	1.37 (12.29)	5.58 (8.16)	4.49 (15.21)	1.26 (12.76)
	5.96 (11.66)	4.28 (7.85)	1.40 (14.15)	5.53 (8.03)	4.26 (13.66)	1.31 (9.9)
	6.16 (8.49)	4.29 (9.0)	1.46 (12.85)	5.47 (6.47)	4.40 (12.76)	1.26 (13.91)
Bet.-lot	6.07	4.34	1.41	5.53	4.38	1.28
%CV	1.66	2.93	3.11	1.01	2.69	2.46
Total						
Mean	6.07	4.34	1.41	5.53	4.39	1.28
%CV	8.96	10.18	5.83	7.12	13.08	11.59
Geomean	6.04	4.32	1.40	5.51	4.35	1.27
T/R						
Mean	1.10	0.99	1.10			
Goemean	1.10	0.99	1.10			
p-value	0.000331	0.75045	0.012474			

Agency Comment #2.
The data showed no drug deposition below the top stage of the cascade impactor. In the FDA's experience with the aqueous nasal sprays, low but measurable levels of drug are observed below the top stage of the impactor. The factors, which may improve deposition in the lower stage include (1) development and use of an assay with greater sensitivity and (2) the use of an atomizing chamber different from the USP throat recommended for oral inhalation products. The revised draft Nasal BA/BE guidance issued on April 2003 recommends the use of a 2L or larger flask. Hence, please repeat the test considering the recommendations made in the guidance. Please provide the detailed methodology of Cascade impaction (test, including the operating parameters).

Firm's response:
Determination of drug in small particle size/ droplet by cascade impactor was repeated as recommended by the Agency. A 5L flask was used instead of the conventional induction port and the resultant data indicate similar deposition below the top stages for the test product and the Reference Listed Drug. The results are presented below in Table 2.

Reviewer's Comment:
The firm has provided some information on the methodology for calculating different parameters used for the Cascade Impactor (PD-113, Issue #2, Attachment #4, vol.4.1). The information for the Operation of the Automated Spray Pump Actuation System has also been provided (GM-143, Issue #7, Attachment #6, Vol. 4.1).

The cascade impaction experiments were conducted using the (b) (4) Cascade Impactor operated at the recommended flow rate of 28.3L. The atomization chamber was a 5L round bottom flask. In each experiment 14 sprays of the test or reference product were used. The amount of calcitonin deposited at the various components of the impactor was determined using an HPLC assay with calibration range of 0.21 – 1.05 mcg/mL. The amount of calcitonin mass was also reported in terms of total mass balance. However, the detailed procedure for calculating the Mass Balance values using the actual data for the test and reference products has not been provided.

TABLE 2
CASCADE IMPACTION

	Test Product		Reference Product	
	GRP-1	GRP-2 + 3	GRP-1	GRP-2 + 3
Within-lot (%CV)	426.46 (3.23)	2.90 (475.17)	468.51 (3.65)	3.43 (497.85)
	411.72 (6.13)	2.39 (1057.12)	456.15 (2.41)	2.49 (440.96)
	418.69 (2.20)	3.17 (291.17)	449.80 (4.17)	1.89 (994.19)
Bet.-lot	418.96	2.82	458.15	2.60
%CV	1.76	14.06	2.08	29.93
Total				
Mean	418.96	2.82	458.15	2.60
%CV	4.27	59.17	3.78	65.54
Geomean	418.58	2.34	457.84	2.12
T/R				
Mean	0.9144	1.082		
Goemean	0.9142	1.105		
p-value	3.50991E-10	0.599		

Even though the T/R ratio for cascade impaction testing are within 90-111%, the cascade impaction testing is incomplete, because the firm did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance data of the cascade impactor runs for the test and reference products.

Agency Comment #3.
The in vitro testing conducted on plume geometry is deficient. SOP for Plume Geometry measurements should be provided. The test/ref ratios of the geometric means for plume angles are within the acceptable limits of 0.9 - 1.11. However, the width measurements are not acceptable, because they do not appear to represent the observed width of the plume. Furthermore, it not clear, if all measurement were made at the same distance from the orifice.

Based on the submitted data, the T/R ratio of geometric means of spray width (based on plume geometry) were in the range of 1.03-1.07. These data suggest that the width of the test product spray is similar to that of the reference product.

On the other hand, T/R ratios for Dmax (based on spray pattern) were in the range of 1.22 - 1.29, which indicates that the width of the test product spray pattern is considerably greater than that of the reference product. Please

explain these results, given that the same technique ([redacted] (b) (4)) was used for both plume geometry and spray pattern analyses.

To impart objectivity to the width measurements, the width should be measured at a fixed distance from the actuator orifice. As recommended in April 2003 draft Nasal BA/BE guidance, the width should be measured at the greatest distance chosen for the spray pattern analysis (5 cm for the present study). Plum geometry SOP should provide details methodology, including the criteria employed for defining the limits of the spray width.

Firm's response:
Plume geometry analysis was repeated and the data demonstrate a ratio of geometric means for the plume angle and plume width within the acceptable limits of 0.9 to 1.11. The plume angle and plume width were determined visually from a single snapshot taken in the fully formed region of the spray (80 msec.). The gradient palette in the [redacted] (b) (4) software was used for analysis. The plume angle measurements were made at the orifice of the actuator tip and the plume width measurements were made at a vertical distance of 6 cm from the actuator tip orifice. The distance represents the greatest distance selected for the spray pattern analysis.

The reason the T/R ratio for Dmax based on the spray pattern analysis was greater than the T/R ratio for plume width based on plume geometry analysis, given that the same [redacted] (b) (4) characterization system was used, may be due to the difference in the analysis technique. First, spray pattern is determined by averaging the images of the entire spray whereas the plume geometry is determined from a single snapshot at a delay time in the fully formed plume region. The software compensates for the background noise when images are averaged but not compensate for background noise when analyzing a single frame. Second, the plume width was not measured at the greatest vertical distance chosen from the spray pattern analysis (i.e. 5 cm for the initial submission). In the original submission, the width was determined at a vertical distance where the spray particles were intense. This distance was closer to the orifice of the actuator tip (i.e. 2 to 3 cm). The width measurement itself was determined based on the outer edges of the more intense particle region (i.e. intensity profile window indicated a minimum 50% intensity) rather than on the outer edges of the actual plume (i.e. intensity profile window indicates a minimum 5 to 10% intensity).

Reviewer's Comment:
The firm has provided methodology, SOP dated June 24, 2003 (Vol.4.1, p.58, Attachment #7) for the Characterization of Plume Geometry for Nasal Spray using [redacted] (b) (4) Spray Characterization System.

The T/R ratios for Plume Geometry (both arithmetic mean and geometric means) are within the acceptable range of 99-111%. Therefore, the in vitro testing on

Plume Geometry is meeting the Agency's acceptable criteria. The Plume Geometry results are presented below:

TABLE 3
PLUME GEOMETRY

	Test Product		Reference Product	
	Plume Angle	Plume Width	Plume Angle	Plume Width
Within-lot (%CV)	86.28 (2.58)	71.30 (3.12)	83.13 (1.41)	66.93 (1.75)
	87.96 (3.24)	73.38 (3.89)	83.41 (2.37)	67.28 (2.93)
	88.74 (2.85)	75.70 (3.34)	83.15 (1.10)	66.38 (1.37)
Bet.-lot	87.66	73.46	83.23	66.86
%CV	1.43	3.00	0.19	0.68
Total				
Mean	87.66	73.46	83.23	66.86
%CV	3.05	6.71	1.66	2.74
Geomean	87.62	73.30	83.22	66.84
T/R				
Mean	1.05	1.10		
Goemean	1.05	1.10		
p-value	1.84164E-08	2.16674E-06		

The SOP (GM-143) for Automated Spray Pump Actuation stations provides tables for Pump-specific parameters for (1) Automated Spray Pump Actuation station and (2) Enhanced Spray Pump Actuation Station. It is not clear which parameters were used for the comparative in vitro testing. Furthermore, it is not clear if the same parameters were used for testing on the test and reference products. The firm should provide this information.

II. Amendment dated January 31, 2005:

In an amendment dated January 31, 2005, the firm proposed to market an additional bottle size (3.7 mL fill volume, 30 actuations). To support the proposal, the firm manufactured one batch of this new fill volume at (b) (4) facility. As per the DBE's recommendation, the firm has provided data on Unit Dose (Unit Spray Content) and Droplet Size Distribution.

The reviewer has searched for the basis of approval of the 3.7 mL RLD product. The product was approved based on the Guidance for Industry dated July 2002, "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation" without additional pharmacokinetic or clinical data. A summary of the approval information is enclosed (Attachment 1).

Regarding the new Fill size, the firm has provided the following information:

- There is no change in the bulk Master Formula. The formulations for the 2 mL and 3.7 mL fill sizes remain the same.
- The new fill volume uses a different bottle (5 mL).The manufacturer is the same as that of the bottle used for the 2 mL product.
- The new fill volume uses the same pump but a longer dip tube. The manufacturer is the same as that of the pump used for the 2 mL product. The only difference between the 2 and 3.7 mL fill size products are the physical dimensions of the dip tube.
- New labeling for the new fill volume has been generated. Copies of the RLD labeling are provided in Attachment No. 26, Vol.1.1, p359-367 (submission dated January 31, 2005). An annotated side-by-side comparison of the proposed 3.7 mL labeling and the RLD labeling are provided in Attachment No. 27, Vol.1.1, p368-392.

Test and Reference Products:

Priming: Both the test and reference products require 6 actuations to produce the spray content NLT 90% of the label claim (based on the firm's response in Attachment No. 20, submission dated January 31, 2005).

Spray Content Uniformity Through Container Life: Assay results from spray 6 (beginning) and spray 35 (end) constitute dose uniformity through container life. Both test and reference products produced average assay values NLT 90% over the container life (see Attachment No. 20,).

Unit Dose (Unit Spray Content) Data

Prod	Sec.	Arith. Mean (N=10)	Geo. Mean	(CV%)	p- value
TEST	BEG	92.85	92.82	2.41	
	END	94.46	94.41	3.40	
REF	BEG	94.49	94.45	2.97	
	END	98.21	98.20	1.35	
TEST/REF	BEG	0.98			0.17
	END	0.96			0.01

Beg = Spray #6
End = Spray #35

Reviewer's Deficiency Comments:

The single actuation content data indicates that the amount of drug /actuation delivered by the test product is within the 90-111% of that delivered by the reference product.

However, the 3.7 mL product fails to meet recommendations for priming given in the draft Nasal BA/BE Guidance. The Nasal BA/BE Guidance recommends: "*For ANDAs, priming would be established providing that the geometric mean emitted dose calculated from the SAC data at B life stage falls within 95-105 percent of label claim.*"

Based on the submitted data the 3.7 mL test product fails to meet the above recommendation. It is noteworthy that the 2 mL test product met the priming recommendation.

The firm should also indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, the firm should provide the information regarding the manufacturer and the automated actuator settings.

Droplet Size Distribution:

Droplet Size Distribution for the test and reference products was determined by Laser Diffraction Method. Droplet size determination was performed on 10 units of Apotex's Batch No. GP7146 and RLD Lot No. H4015. Each unit was tested at beginning and end sectors of unit life. At each sector of unit life, each unit was actuated at two distances (3 cm and 6 cm) relative to the laser beam. At each distance, measurements were taken at three delay times. The three delay times characterize three regions in the plume life based on % transmission:

Plume Region	Transmission Characteristic
Plume formation (Initial)	Drops
Fully formed plume (Middle)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling points on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distances. The firm submitted D10, D50, D90 and SPAN data for the fully formed plume. Based on the revised draft of the Nasal BA/BE guidance, bioequivalence evaluation is based only on D50 and SPAN data at the fully formed plume (Middle). A summary of these data based on the reviewer's calculations is presented below:

Droplet Size Distribution - D50 Data

PROD.	Stage	Distance (cm)	Mean Arith (N=10)	Geo (N=10)	Variability (%CV) Total (N=10)	TEST/REF Geo.	P-value
TEST	BEG	3	47.24	47.07	8.93	0.97	0.54
	END	3	48.0	47.77	10.18	0.98	0.64
TEST	BEG	6	47.21	47.14	5.60	1.02	0.29
	END	6	47.55	47.50	4.70	1.02	0.38
REF	BEG	3	48.61	48.38	9.74		
	END	3	48.90	48.82	6.01		
REF	BEG	6	46.21	46.15	4.85		
	END	6	46.69	46.67	3.25		

Droplet Size Distribution - Span Data

PROD.	Stage	Distance (cm)	Mean Arith (N=10)	Geo (N=10)	Variability (%CV) Total (N=10)	TEST/REF Geo.	P-value
TEST	BEG	3	1.62	1.62	2.66	1.04	0.01
	END	3	1.59	1.59	3.28	1.02	0.17
TEST	BEG	6	1.32	1.31	6.67	0.99	0.69
	END	6	1.34	1.34	6.74	0.98	0.47
REF	BEG	3	1.55	1.55	2.59		
	END	3	1.56	1.55	2.27		
REF	BEG	6	1.33	1.33	6.72		
	END	6	1.37	1.37	6.10		

Representative Time History Plots on Particle Size Distribution are presented below:

Attachment for figures for Particle Size Distribution


GP7146-6.pdf


GP7146-4.pdf

(T)


H4015-5.pdf


H4015-7.pdf

(R)

Reviewer's Comments on Droplet Size Distribution:

1. Evaluation of the comparative droplet size distributions by laser diffraction: Based on the geometric mean plume data, the T/R ratios for D50 and SPAN are within the 0.9-1.11 range, used hitherto by DBE for acceptance of solution nasal spray products.

2. For D50 and SPAN, the variability for the test product is comparable to that of the reference product.

Deficiency Comments:

1. Based on the Standard Operating Procedure (SOP) submitted, it is not clear what automated actuator parameters (settings) were used for the 2 mL fill size product, and if the settings were same for the test and reference products. The firm should provide this information.

2. The 3.7 mL product fails to meet recommendations for priming given in the draft Nasal BA/BE Guidance. The draft CDER Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" recommends: "*For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-105 percent of label claim.*" It is noted that the 2 mL test product met this recommendation.

3. The firm should indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, the firm should provide the name of the manufacturer and the details of the automated actuator settings.

4. The cascade impaction testing for the 2 mL fill product is incomplete, because the firm did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance of the cascade impactor runs for the test and reference products.

Recommendations

1. The in vitro performance data submitted by Novex Pharma for its Calcitonin-salmon Nasal Spray, 200 IU/spray in the 2 mL product is incomplete due to the deficiency in the priming as mentioned in the deficiency comments above.

2. The in vitro performance data submitted by Novex Pharma for its Calcitonin-salmon Nasal Spray, 200 IU/spray in the 3.7 mL product is incomplete due to the deficiency in the priming as mentioned in the deficiency comments above.

Sikta Pradhan 8/9/05

Sikta Pradhan, Ph. D, Date
Review Branch IV

Dhariwal 8/9/2005

Kuldeep R. Dhariwal, Ph. D. Date
Team Leader, Review Branch IV

Dale P. Conner 8/9/05

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCY DEFICIENCIES

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray
2 mL Product and 3.7 mL Product

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The 3.7 mL product fails to meet recommendations for priming given in the CDER draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action." This guidance recommends: "For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-105 percent of label claim." It is noted that your 2 mL product met that recommendation.
2. Please indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, please provide the name of the manufacturer and the details of automated actuator settings.
3. Based on the Standard Operating Procedure (SOP) submitted, it is not clear what automated actuator parameters (settings) were used for the 2 mL fill size product, and if the settings were same for testing the test and reference products. Please provide this information.
4. The cascade impaction data for the 2 mL fill size product are incomplete because you did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance of the cascade impactor runs for the test and reference products. Please provide the requested information.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-396
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

Printed in final on 8/9/05

Endorsments: (Final with Dates)
HFD-650/ S. Pradhan
HFD-650/ K. Dhariwal 8/9/05
HFD-655/ G. Singh 8-9-05
HFD-650/ D. Conner 8/9/05
HFD-650/ Fritsch

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BIOEQUIVALENCE: Deficiencies

✓ 1. IN VITRO BIO STUDY AMENDMENT — Submission date: 07-29-04
Nasal Spray, 200 IU/spray , 2 mL Product — Outcome IC

✓ 2. IN VITRO BIO STUDY AMENDMENT — Submission date: 01-31-05
Nasal Spray, 200 IU/spray , 3.7 mL Product — Outcome IC

OUTCOME DECISIONS: **IC** - Incomplete

Attachment 1.

Miacalcin® (Calcitonin Salmon Nasal Spray) Spray
NDA 20-313

The prior approval supplemental application (NDA 20-313, SCS-023, 4/21/2003) provides for a new size 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 (2 mL).

As per the NDA Chemist's Review, no changes are planned concerning the glass vial quality and supplier, the drug solution (composition and manufacturing), the rubber stopper, the flip tear-off cap and the nasal pump.

Following in vitro testing was performed to support the change in size of the vial:

Priming/Pump Delivery/Tail Off: Each spray vial was weighed and holding it in an upright position. Each pump was actuated mechanically by a (b) (4) robot using a force of 60 N. The weight of liquid expulsed was determined 29 times for the current spray and 49 times for the new size vial.

Number of Primers: For each spray container the number of actuations before a dose of 85% of label claim (77 mg) or more is obtained was counted. About 2/3 pumps needed only 4 primers to deliver >=85% of the target dose at the 5th actuation. Most of the new vials needed 5 primers instead of 4. The OCPB reviewer concluded that it is difficult to set a fixed number of primers since the patient leaflet states that "The pump is primed once the first full spray is emitted." There was no change from the previous recommendation.

Pump Delivery: For each spray container the number of actuations delivering a full dose after priming, e.g. 85-115% of label claim (77-105 mg), was counted. With the current vial, in most cases at least 18 full actuations were counted with a minimum of 16 actuations, meeting the requirement of 14 full doses.

With the proposed vial, at least 37 full actuations were counted with a minimum of 34 actuations. The proposed delivery of 30 full does was met.

Tail-Off Profile: The tail-off profile curves were similar for the smaller and the proposed vials. Testing complied with the Nasal Spray Guidance and the results were adequate.

Osmolality: The osmolality of test solutions from 3 vials from 3 batches were measured by freezing-point depression. Mean osmolality of the drug solution was 271 mosmol/kg. Since the solution formulation is not changed, no change in osmolality is expected.

Spray Content Uniformity (determined by gravimetry): For three batches of the new vials, 10 vials were selected and equipped with spray pumps. Each pump was actuated 5 times to prime it and then the weight of spray on the first, fifteenth and thirtieth full actuation was determined. The mean amount of calcitonin delivered was 208 I.U. The results were adequate.

Spray Content Uniformity (determined by HPLC): The spray content of calcitonin by HPLC and by weight were shown to be linear correlated with a slope of 1.04 and correlation coefficient of 0.992.

Droplet Size (determined by laser light diffraction): Droplet size from actuation until the end was determined by (b) (4) device. Results showed higher values for droplet size at the beginning and at the end due to incomplete priming at the start and the emptying container at the end. Excluding these values, statistical distributions were calculated showing for each spay the the droplet size at 10, 50 and 90% of the distribution (i.e. D10, D50 and D90). The variability within each pump was small with coefficient of variations less than 2%. The variability was greater between pumps of the same batch or between batches. Testing and results were adequate.

Spray Pattern: Ten samples from three batches of new vials were fitted with spray pumps. After six actuations (priming), the 1st, 2nd, 5th, 16th, 29th, and 30th actuations were collected on TLC plates. Spray pattern was not circular since the mean Dmin=17.6 mm, Dmax=22.0 mm, and Ratio Dmax/Dmin=1.3. Testing and results were adequate.

The supplemental application was approved by the Agency on August 22, 2003.

DEC 5 2005

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-396
Drug Product Name	Calcitonin-Salmon Nasal Spray,
Strength	200 IU/Spray, 2 mL fill volume and 3.7 mL fill volume
Applicant Name	Novex Pharma Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	
Amendment Date(s)	August 18, 2005 September 1, 2005
Reviewer	Sikta Pradhan
First Generic	No
File Location	V:\firmsnz\Novex\ltrs&rev\76396A0905.Doc

Review of Amendments

Executive Summary

These amendments (dated August 18, 2005 and September 1, 2005) are in response to the deficiencies of the in vitro testing with respect to priming and cascade impaction testing for the test products, 3.7 mL and 2.0 mL fill sizes, respectively, communicated to the firm by the Division of Bioequivalence (DBE).

All in vitro performance data submitted in this application have been analyzed using the Population Bioequivalence Methodology. All in vitro testing meets the acceptance criteria, with the exception of spray pattern ovality. The firm is asked to requantitate the spray patterns using automation or repeat the test.

The application is incomplete.

Amendments Reviewed

I. **Amendment dated August 18, 2005. –** Response to the Agency comments on priming of the test product, 3.7 mL fill volume and cascade impaction testing of the test product, 2.0 mL fill volume.

II. **Amendment dated September 1, 2005.** – Response to the Agency comments on cascade impaction testing of the test product, 2.0 mL fill volume

I. Amendment dated August 18, 2005.

Agency Comment #1.

The 3.7 mL product fails to meet recommendations for priming given in the CDER draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action." This guidance recommends: "For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B life stage falls within 95-105 percent of label claim." It is noted that your 2 mL product met that recommendation.

Firm's response:
The priming data for the 3.7 mL product that failed to meet the 95-105% limit stated in the draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", was performed on 10 bottles. This test has been repeated on 30 bottles as recommended in the draft guidance. The geometric mean of the spray content uniformity results from the 30 bottles at the beginning life stage (6th spray) falls within 95 – 105% of label claim. Based on this data, priming was established after the pump had been actuated five times.

Assay per Spray At Beginning Life Stage (Spray #6) for Batch No. GP7146, Apotex Inc.		
Bottle No.	Weight (g)	Assay (%)
1	(b) (4)	

	(b) (4)
Mean:	96
Min:	(b) (4)
Max:	

Reviewer's Comment: The firm's response is acceptable.

Agency Comment #2.

Please indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, please provide the name of the manufacturer and the details of automated actuator settings.

Firm's response:
An (b) (4) Automatic Spray Pump Actuation Station was used for the determination of Unit Spray contents for both the test and reference products. A copy of the test method GM-143 which contains the details of the actuator settings was included in Attachment 21 of the Major Amendment dated January 31, 2005. The details of the settings are provided below for your convenience.

Actuator Settings of The (b) (4) Spray Pump Actuation Station for the Calcitonin Nasal Spray Pump ((b) (4))	
Parameters	Settings
Dose Time (msec)	20 ± 2
Return Time (msec)	30 ± 5
Hold Time (sec)	0.5
Actuation Force (kg)	6.0 ± 0.5

Reviewer's Comment:
The firm's response is acceptable.

Agency Comment #3.
Based on the Standard Operating Procedure (SOP) submitted, it is not clear what automated actuator parameters (settings) were used for the 2 mL fill size product, and if the settings were same for testing the test and reference products. Please provide this information.

Firm's response:
For the 2 mL fill size product, the same (b) (4) actuation station and settings, as described in the response to question 2 above, were used for both the test and reference products.

Reviewer's Comment:
The firm's response is acceptable.

Agency Comment #4.
The cascade impaction data for the 2 mL fill size product are incomplete because you did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance of the cascade impactor runs for the test and reference products. Please provide the requested information.

Firm's response:

Due to the limited capacity for text in SAS, the units of the comparative data in Group 1, 2 and 3 and the data supporting mass balance may not have been clearly identifiable. Please refer to the Table entitled "Summary of Droplet Size Distribution by Cascade Impactor for Calcitonin Salmon" provided as Attachment No.3, which clearly provides the unit of measure (i.e. microgram/stage), as well as the mass balance data (described as "Material Balance"). Please note the data provided in Attachment No. 3 is the same as that provided in SAS.

Reviewer's Comment:
The firm's response was not acceptable with respect to the mass balance data and therefore the firm was asked to provide responses to additional comments. The firm's response to the comments was provided in the amendment dated September 1, 2005 (see below).

II. Amendment dated September 1, 2005.

Agency Comment #1.
Provide a table containing the comparative data for cascade impaction for groups 1, 2 & 3 including the units.

Firm's response:
As requested, comparative data for cascade impaction for groups 1, 2, and 3 including the units is provided in Tables 1 and 2 of Attachment No. 2 for the test and reference products, respectively.

Reviewer's Comment:
The firm's response is acceptable.

Agency Comment #2.
Explain how the mass balance data were derived from the raw data of cascade impaction for both the test and reference.

Firm's response:
The mass balance data in Tables 1 and 2 of Attachment No.2 were derived by the following formula:

$$\text{Material Balance (\%)} = \frac{\text{Deposited Amount (µg) x 100}}{\text{Actual Amount (µg)}}$$

The Deposited Amount is derived by HPLC analysis of samples collected as per sections 5.4.8 to 5.4.10 of test method PD-113 (presented in Attachment No. 5 of Amendment dated July 29, 2004).

Reviewer's Comment:

Given below are the tables summarizing the cascade impaction testing:

Table 1.PDF

Table 2.PDF

Following this page, 2 pages withheld in full (b)(4)

Agency Comment #3.
Provide mass balance data for the test and reference products.

Firm's response:
Mass balance data for the test and reference products is provided in Tables 1 and 2 of Attachment No.2, respectively. Please note that the term "Material Balance" is used in place of "Mass Balance" in Tables 1 and 2.

Reviewer's Comment:
Mass Balance (%) for the test and the reference are in the range of 87.03-97.74 and 88.25-99.39, respectively. The reported mass balance values are within 85-115% acceptance range as stated in the nasal BA/BE Guidance.

The cascade impactor data were analyzed using population BE Method. Based on these analyses, drug deposited in group 2+3 (< 9 micron) meets the acceptance criteria (see attachment).

The firm's response is acceptable.

Population Bioequivalence Analyses of ALL In Vitro Performance Data

On August 3, 2005, the DBE management made a decision to implement the draft Population Bioequivalence (PBE) method that was developed for evaluation of certain comparative in vitro performance studies on aerosols and nasal sprays. All comparative data submitted in this application up to now were analyzed using the PBE method as outlined in the June 1999 draft Nasal BA/BE guidance. These analyses used a $sigma_{T0}$ of 0.1 and epsilon of 0.01.

The results of the PBE analyses demonstrate equivalence of in vitro performance between the test and reference products for all comparisons (see attached documents below), *with the exception of ovality ratio of the Spray Patterns.*

All initial testing was performed on the 2mL fill size of the test and reference products. However, the RLD introduced a 3.7 mL fill (Supplement Approval Date: August 22, 2003) without changing the formulation and the delivery system. Therefore, Novex Pharma wanted to include a 3.7 mL fill employing the same formulation and delivery system as used in its 2 mL product. The only difference between the 2 mL and the 3.7 mL products is the size of the container bottle and the length of the dip tube. The firm sent a controlled correspondence (04-196) requesting in vitro testing requirements for the 3.7 mL product, which contained the same formulation and used the same delivery system as the 2 mL product. The DBE provided its response through a telecon on September 24, 2004, requesting the firm to determine priming characteristics of its 3.7 mL product and compare it with the RLD at Beginning and End sectors for Single Actuation Content (Content uniformity) and droplet size distribution by laser diffraction. The data for the latter two studies was analyzed by the PBE

methodology and it meets equivalence criteria (attachment). The priming data are reviewed herein and found acceptable.

Correction of Spray Pattern Data reported in the previous review (stamp date: 08/09/05).

The spray pattern data were previously reviewed and considered acceptable based on the ratios of geometric means and comparative variability of the Test (equal to or less than Reference). However, based on recent PBE analyses of the data, spray pattern ovality failed to meet the acceptance criteria. Upon examination of the previous excel calculations, a mistake was revealed in the calculation of total variability for ovality. The revised data are presented in Table 3 below:

TABLE 3. SPRAY PATTERN (containing corrected Ovality data)

	Test Product			**Reference Product**		
3 Cm						
	Dmax	Dmin	Oval. Ratio	Dmax	Dmin	Oval. Ratio
Within-lot (%CV)	4.05 (7.20)	3.32 (14.54)	1.24 (12.81)	3.81 (8.25)	3.34 (9.59)	1.14 (4.06)
	4.02 (10.54)	3.25 (10.28)	1.24 (10.37)	3.72 (4.16)	3.25 (7.57)	1.15 (5.64)
	4.14 (8.69)	3.36 (6.15)	1.24 (9.62)	3.69 (6.57)	3.30 (8.21)	1.12 (7.43)
Bet.-lot	4.07	3.31	1.24	3.74	3.30	1.14
%CV	1.53	1.68	0.33	1.67	1.37	1.18
Total						
Mean	4.07	3.31	1.24	3.74	3.30	1.14
%CV	8.68	10.57	***10.63****	6.50	8.30	5.73
Geomean	4.05	3.29	1.23	3.73	3.29	1.14
T/R						
Mean	1.09	1.00	1.09			
Goemean	1.09	1.00	1.08			
p-value	0.000386	0.877298	0.001977			
	Test Product			**Reference Product**		
6 Cm						
	Dmax	Dmin	Oval. Ratio	Dmax	Dmin	Oval. Ratio
Within-lot (%CV)	6.08 (6.84)	4.49 (12.88)	1.37 (12.29)	5.58 (8.16)	4.49 (15.21)	1.26 (12.76)
	5.96 (11.66)	4.28 (7.85)	1.40 (14.15)	5.53 (8.03)	4.26 (13.66)	1.31 (9.9)
	6.16 (8.49)	4.29 (9.0)	1.46 (12.85)	5.47 (6.47)	4.40 (12.76)	1.26 (13.91)
Bet.-lot	6.07	4.34	1.41	5.53	4.38	1.28
%CV	1.66	2.93	3.11	1.01	2.69	2.46
Total						
Mean	6.07	4.34	1.41	5.53	4.39	1.28
%CV	8.96	10.18	***12.93****	7.12	13.08	11.59

	Geomean	6.04	4.32	1.40	5.51	4.35	1.27
T/R							
	Mean	1.10	0.99	1.10			
	Goemean	1.10	0.99	1.10			
	p-value	0.000331	0.75045	0.012474			

* 4.12 and ** 5.83 reported in the previous review (stamped dated August 9, 2005).

Based on these data, the ovality ratio of the test product is considerably more variable than those of the reference product, and the estimates of variability is the same as $Sigma_T$ and $Sigma_R$ noted in the PBE analyses. Therefore, even though the ratios of geometric means are in the acceptable range of 90-111, the test product fails to meet equivalence (based on the PBE analysis) of spray pattern ovality, because of its considerably greater variability.

DEFICIENCY COMMENTS:

The results of the PBE analyses also demonstrate equivalence between the test and reference products for all comparisons, *with the exception of ovality ratio of the Spray Patterns.*

It is noted that the firm has conducted manual quantitation of spray patterns. The firm may repeat the spray pattern quantitation using a computerized method measuring area and ovality ratios of spray patterns, to avoid variability imparted by manual/subjective quantitation of the results. For automated quantitation of spray patterns, equivalence will be based on the area and ovality ratio based on *true* shapes of the spray patterns. The data should be analyzed using the PBE method employing $sigma_{T0}$ of 0.1 and epsilon of 0.01. The acceptance limits for the 90% confidence intervals comparing the test and reference products is 90-111%.

The firm also has the option of repeating the test using non-impaction (laser sheet) methods. Equivalence of spray patterns of test and reference products by such methods is also based on the spray pattern area and ovality ratio data. If the testing is repeated, it should be performed on the same batches of the test and reference products, if the batches are still within the expiration date. If they have expired, the test should be performed using three new batches of the test and reference products.

PBE analysis (NOT TO BE RELEASED UNDER FOI):

2 mL Fill Volume


CI_GROUPS ?AND3.doc (7 KB)


CI_GROUP 1.doc (7 KB)


CI_GROUP 2.doc (7 KB)


CI_GROUP 3.doc (7 KB)


Plume_ANGLE.doc (12 KB)


Plume_WIDTH.doc (12 KB)


Spray_3cm_DMAX.doc (13 KB)


Spray_3cm_DMIN.doc (13 KB)


Spray_3cm_OVALITY.doc (13 KB)


Spray_6cm_DMAX.doc (13 KB)


Spray_6cm_DMIN.doc (13 KB)


Spray_6cm_OVALITY.doc (13 KB)

2.0 mL Fill Volume


DSD_SPAN_DIST8.doc (18 KB)


DSD_D50_DIST3.doc (17 KB)


DSD_D50_DIST5.doc (17 KB)


DSD_D50_DIST8.doc (17 KB)


DSD_SPAN_DIST3.doc (19 KB)


DSD_SPAN_DIST5.doc (19 KB)


UD_.doc (17 KB)

3.7 mL Fill Volume


DSD_6cm_SPAN ?IST6.doc (13 KB)


DSD_3cm_SPAN ?IST3.doc (13 KB)


DSD_3cm_D50_)IST3.doc (10 KB


DSD_6cm_D50_)IST6.doc (10 KB


SAC_.doc (10 KB)

Recommendation

The in vitro performance data submitted by Novex Pharma for its Calcitonin-salmon Nasal Spray, 200 IU/spray in 2 mL fill volume is incomplete as the spray pattern ovality data analyzed by the PBE approach did not meet the acceptance criterion.

Sikta Pradhan 12/5/05

Sikta Pradhan, Ph. D, Date
Review Branch IV

K Dhariwal 12/5/2005

Kuldeep R. Dhariwal, Ph. D. Date
Team Leader, Review Branch IV

Dale P. Conner 12/5/05

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCIES

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray
2 mL Product and 3.7 mL fill sizes

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The in vitro performance data are incomplete because spray pattern ovality fails to meet the acceptance criteria due to high variability of the test product compared to the reference product.

It is noted that you have conducted manual quantitation of spray patterns. To reduce variability in measurements, you may repeat the spray pattern quantitation using an automated/computerized method measuring area and ovality ratios of spray pattern images. The revised data should be analyzed using the Population Bioequivalence Method employing $sigma_{T0}$ of 0.1 and epsilon of 0.01.

You also have the option of repeating the test using a non-impaction (laser-sheet) method. Equivalence of spray patterns of test and reference products by such methods is also based on the spray pattern area and ovality ratio data, based on the true pattern shapes. If the test is repeated, it should be performed on the same batches of the test and reference products, if the batches are still within the expiration date. If they have expired, the test should be performed using three new batches of the marketed test and the available reference products.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-396
ANDA DUPLICATE
DIVISION FILE
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Printed in final on 12/5/2005

Endorsments: (Final with Dates)
HFD-650/ S. Pradhan
HFD-650/ K. Dhariwal 12/5/05
HFD-655/ G. Singh 12-5-05
HFD-650/ D. Conner 12/5/05
HFD-650/ Fritsch

V:\Firmsnz\Novex\ltrs&rev\76396A0905

BIOEQUIVALENCE: Deficiencies

✓ 1. IN VITRO BIO STUDY AMENDMENT — Submission date: 08-18-05
Nasal Spray, 200 IU/spray , 2 mL Product — Outcome IC

✓ 2. IN VITRO BIO STUDY AMENDMENT — Submission date: 09-01-05
Nasal Spray, 200 IU/spray , 3.7 mL Product — Outcome IC

OUTCOME DECISIONS: **IC** - Incomplete

MAY 15 2006

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-396
Drug Product Name	Calcitonin-Salmon Nasal Spray,
Strength	200 IU/Spray, 2 mL fill volume and 3.7 mL fill volume
Applicant Name	Novex Pharma Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	April 5, 2006
Amendment Date(s)	
Reviewer	Sikta Pradhan
First Generic	No
File Location	V:\firmsnz\Novex\ltrs&rev\76396A0406.Doc

Review of Amendments

Executive Summary

This amendment (dated April 5, 2006) is in response to the deficiencies of the in vitro testing with respect to spray pattern testing for the test products communicated to the firm by the Division of Bioequivalence (DBE). In the current amendment the firm has responded to the Agency comments.

The firm's response is acceptable. The spray pattern ovality data analyzed by the Population Bioequivalence (PBE) approach meets the acceptance criterion of 0.9 – 1.11. The application is acceptable.

Amendments Reviewed

Agency Comment #1.

The in vitro performance data are incomplete because of the spray pattern ovality fails to meet the acceptance criteria due to high variability of the test product compared to the reference product.

It is noted that you have conducted manual quantitation of spray patterns. To reduce variability in measurements, you may repeat the spray pattern quantitation using an automated/computerized method measuring area and ovality ratios of spray pattern images. The revised data should be analyzed using the Population Bioequivalence Method employing σ_T of 0.1 and epsilon of 0.01.

You also have the option of repeating the test using a non-impaction (laser-sheet) method. Equivalence of spray patterns of test and reference products by such methods

is also based on the spray pattern area and ovality ratio data. If the test is repeated, it should be performed on the same batches of the test and reference products, if the batches are still within the expiration date.

Firm's response:

The firm has repeated the spray pattern test using the impaction thin layer chromatographic method with manual analysis. The test was performed on three different batches of the reference product (Batch Nos.-Expiry Date: H5018A-07/08, H5020A-08/08, H5021A-09/08) and three new lots of Apotex product (Lot Nos.:HC3917, HC3918 and HC3939). It is believed that the higher variability in the spray pattern data observed with the Apotex product in the previously submitted data, causing the product to fail the PBE criterion, was due to the use of different lots of pump in the 3 batches of the Apotex product, and the likelihood that the three batches of RLD product utilized the same lot of pump (due to the fact that all three batches had the same expiry date). As a result, three batches of reference product, with different expiry dates, were chosen to try to ensure that different batches of pumps, as with the Apotex product, were likely to exist among the batches in order to provide a proper comparison of the two products. This was agreed to by the Agency during the telephone conference on December 22, 2005. The spray pattern Dmax and ovality ratio data were analyzed using the Population Bioequivalence Method employing σ_T of 0.1 and epsilon of 0.01. The results indicate that the spray pattern of Apotex's product is equivalent to that of the reference product as the Population Bioequivalence criterion was met for both Dmax and ovality ratio. The summary of the statistical analysis is provided as Attachment No.3. It is noteworthy that the variability of the data associated with the Apotex product is no longer higher than that of the reference product. This supports firms proposition that the "failure" of firm's previously submitted data was not due to inequivalence of the two products but as a result of inequitable comparison of them. The use of the same testing method as with the previously submitted data also assures that the new data is not due to any change in the testing method.

Comparative Summary of Spray Pattern Test of Calcitonin Salmon Nasal Spray

Strength: 200 IU/dose
Reference Product: Miacalcin (Calcitonin Salmon) 200 IU/dose
Apotex Batch#: GP7146 (Pump#: HC3917, HC3918, HC3939)
Innovator Lot#: H5018A (exp.:07/2008), H5020A (exp.: 08/2008), H5021A (exp.:09/2008)
Test: Spray pattern

Manf.	Lot No.	Pump No.	Beginning Spray					
			Distance =3.0 cm			Distance =6.0 cm		
			Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality
Apotex (Test)	GP7146	HC3917	(b) (4)					
	GP7146	HC3918						
	GP7146	HC3939						
	Mean		3.34	2.82	1.186	4.63	3.87	1.201
	%RSD		2.0	2.2	0.3	3.5	3.0	1.4
	Max.		(b) (4)					
	Min.							
Novartis (Ref.)	H5018A	N/A	(b) (4)					
	H5020A	N/A						
	H5021A	N/A						
	Mean		3.50	2.98	1.177	4.89	3.90	1.268
	%RSD		4.6	4.0	2.0	6.6	8.2	4.5
	Max.		(b) (4)					
	Min.							
	Ratio of Means		0.95	0.95	1.01	0.95	0.99	0.95

Reviewer's Comment:

Population Bioequivalence Analyses of the Spray Pattern Data: All comparative data of the test and the reference products submitted in this amendment were analyzed using the Population Bioequivalence (PBE) method as outlined in the June 1999 draft Nasal BA/BE guidance. These analyses used a $sigma_{T0}$ of 0.1 and epsilon of 0.01.

Manf.	Beginning Spray					
	Distance =3.0 cm			Distance =6.0 cm		
	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality
Apotex (Test)	3.33	2.82	1.18	4.62	3.85	1.20
Novartis (Ref.)	3.49	2.97	1.17	4.86	3.86	1.26
T/R Ratio	0.954	0.947	1.007	0.949	0.998	0.951
90% CI for Ratio	92.8, 98.2	92.0, 97.6	98.0, 103.5	91.6, 98.4	95.1, 104.8	91.3, 99.0
Overall Test Outcome: Fail/Pass	Pass	Pass	Pass	Pass	Pass	Pass

The results of the PBE analyses demonstrate equivalence of in vitro performance between the test and reference products for comparisons (see attached documents below), Dmax, Dmin and *ovality ratios of the Spray Patterns.*

The firm's response to the Agency comment is acceptable.

OVERALL COMMENTS:

1. The results of the PBE analyses of the Spray Patterns data submitted in the current amendment (dated 04/05/06) demonstrate equivalence between the test and reference products for the *ovality ratio of the Spray Patterns.*

2. The composition of the test product is quantitatively and qualitatively the same as that of the reference product (submission dated 04/05/02, 09/11/02 and 06/05/03). The CMC review also indicates that the test product is Q_1/Q_2 to the innovator's formulation based on the information from NDA 20-313/S-18.

3. The firm has previously demonstrated (submission dated 07/29/04, 01/31/05, 08/18/05 and 09/01/05) that the test and reference products are equivalent for all other in vitro comparisons, such as, Priming, Droplet Size Distribution (Laser Diffraction and Cascade Impaction), Plume Geometry and Spray Pattern (with the exception of Ovality ratio of the Spray Patterns).

4. The results of the PBE analyses of the previously submitted data also demonstrate equivalence between the test and reference products for all comparisons.

5. In an amendment dated January 31, 2005, the firm proposed to market an additional bottle size (3.7 mL fill volume, 30 actuations). To support the proposal, the firm manufactured one batch of this new fill volume at (b) (4) (b) (4) facility, and as per the Agency's request (Sept. 24, 2004), the firm has provided data on Unit Dose (Unit Spray Content), Priming and Droplet Size Distribution on that batch. The single actuation content and droplet size distribution data (previously submitted to the Agency) to bridge the 2 mL and 3.7 mL fill sizes were also analyzed by the PBE method. Based on these analyses both data sets met the acceptance criteria.

   Note: In a supplement (NDA #20-313, SCS-023 dated 04/21/03), Novartis Pharmaceutical Corporation expressed its intention of marketing its Miacalcin Nasal spray, 2200 I.U./mL in 3.7 mL fill volume delivering 30 doses instead of the approved 2200 I.U./mL in 2 mL fill volume delivering 14 doses. No other changes were made. This supplement was found acceptable to the Agency.

PBE analysis (NOT TO BE RELEASED UNDER FOI):

C:\ESD#2\Calcitonin\
PBE-Spray.Txt

spray_DmaxDist
3.doc (17 KB)

spray_DmaxDist
6.doc (17 KB)

spray_DminDist3
.doc (17 KB)

spray_DminDist6
.doc (17 KB)

C:\ESD#2\Calcitonin\
Spray_ptn.Txt

Spray_OvalityDis
t3.doc (17 KB)...

Spray_OvalityDis
t6.doc (17 KB)...

RECOMMENDATION

1. The in vitro performance data submitted by Novex Pharma for its Calcitonin-salmon Nasal Spray, 200 IU/spray (2 mL fill volume and 3.7 mL fill volume) are acceptable. With respect to the in vitro testing, Calcitonin-salmon Nasal Spray, 200 IU/spray manufactured by Apotex for Novex Pharma is equivalent to the Innovator product, Miacalcin^{R} Nasal Spray, 200 IU/spray manufactured by Novartis.

Sikta Pradhan 5/15/06

Sikta Pradhan, Ph. D, Date
Review Branch IV

Yih-Chain Huang 5/15/2006

Yih-Chain Huang, Ph. D. Date
Team Leader, Review Branch IV

Barbara M Sawit 5/15/06

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray
2 mL fill volume and 3.7 mL fill volume

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-396
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Endorsments: (Final with Dates)
HFD-650/ S. Pradhan
HFD-650/ Y. Huang 5/15/2006
HFD-650/ D. Conner 5/15/06
HFD-650/ Fritsch

V:\Firmsnz\Novex\ltrs&rev\76396A0406

BIOEQUIVALENCE: Acceptable

1. IN VITRO BIO STUDY AMENDMENT — Submission date: 04-05-06
Nasal Spray, 200 IU/spray,
(2 mL and 3.7 mL bottles) — Outcome AC

OUTCOME DECISIONS: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-396 SPONSOR : Novex Pharma

DRUG AND DOSAGE FORM : Calcitonin-Salmon Nasal Spray,
STRENGTH(S) : 200 IU/ spray (2 mL and 3.7 mL fill size)

TYPES OF STUDIES : In Vitro Tests

CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : See attached review.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic Yes New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Sikta Pradhan, Ph.D. BRANCH : IV

INITIAL : Sikta Pradhan DATE : 5.15.06

TEAM LEADER : Yih-Chain Huang, Ph. D. BRANCH : IV

INITIAL : YCH DATE : 5/15/2006

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : BMD DATE : 5/15/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076396

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 8, 2002

Refuse to receive.
Not Q1/Q2 to RLD.
11-JUN-2002
Gregory S. Davis

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc. of Ontario, Canada, is hereby forwarding an original abbreviated new drug application (ANDA) for Calcitonin-Salmon Nasal Spray, 200 IU/spray.

Enclosed is an archival copy under blue cover, a chemistry review under red cover, and the bioavailability/bioequivalence review section under orange cover and a field copy under a burgundy cover.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
APR 11 2002
OGD / CDER

Bartle, Margo L

From: Bartle, Margo L
Sent: Wednesday, May 15, 2002 8:17 AM
To: Fang, Florence S; Holcombe Jr, Frank O; Patel, Rashmikant M; Sayeed, Vilayat A; Schwartz, Paul
Cc: Liu, Shing Hou
Subject: FIRST GENERIC 76-396

FIRST GENERIC 76-396 CALCITONIN-SALMON NASAL 200 IU/SPRAY NOVEX RECEIVED-11-2002

TEAM LEADER IS SHING LIU

THANKS,

MARGO

The following studies have been identified in this submission. Please verify the appropriate studies and provide the strengths and outcome for each study (please write and circle the appropriate items):

ANDA # 76-596 Submission Date(s): 4.11.02.

1. Fasting study (STF) Strengths: _____
   Outcome:
   AC IC UN NC

2. Food study (STP) Strengths: _____
   Outcome:
   AC IC UN NC

3. Multiple Dose study (STM) Strengths: _____
   Outcome:
   AC IC UN NC

4. Dissolution Data (DIS) All Strengths
   Outcome:
   AC IC UN NC

5. Study Amendment (STA) Strengths: _____
   Outcome:
   AC IC UN NC

6. Waiver (WAI) Strengths: 200 14
   Outcome:
   AC IC UN NC

7. Dissolution Waiver (DIW) Strengths: _____
   Outcome:
   AC IC UN NC

8. Other (OTH)
   Strengths: _____
   Outcome:
   AC IC UN NC

9. Other options (less common): Strengths: _____

   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)
   d. Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)

   Outcome:
   AC IC UN NC

Outcome Decisions:

AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WP File Name (include extension): _____
X:\new\ogdbioeq\memos\biocodes

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : May 15, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 15-MAY-2002

SUBJECT: Examination of the request for waiver submitted with an ANDA for Calcitonin-Salmon Nasal Spray, 200 IU/Spray to determine if the application is substantially complete for filing.

Novex Pharma submitted AND 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Novex on April 8, 2002 for its Calcitonin-Salmon product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

_____ Waiver meets statutory requirements

__V__ Waiver does **NOT** meet statutory requirements W+H 6/10/2002

Reason: The test formulation is not Q1+Q2 with the reference formulation because:

(b) (4)

① Amount of Benzalkonium Chloride:

② amount of Sodium chloride

③ Adjustment of pH:

Director, Division of Bioequivalence

6/10/02
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-396 DRUG NAME Calcitonin-Salmon FIRM Apotex / Novex Pharma

DOSAGE FORM(s) Nasal Spray 200 IU/spray

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	N/A				
Assay Methodology	N/A				
Procedure SOP	N/A				
Methods Validation	N/A				
Study Results Ln/Lin	N/A				
Adverse Events	N/A				
IRB Approval	N/A				
Dissolution Data	N/A				
Pre-screening of patients	N/A				
Chromatograms	N/A				
Consent forms	N/A				
Composition	V				
Summary of study	N/A				
Individual Data & Graphs , Linear & Ln	N/A				
PK/PD data disk	N/A				
Randomization Schedule	N/A				
Protocol Deviations	N/A				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	N/A				
Analytical site	N/A				
Study investigators	N/A				
Medical Records	N/A				
Clinical Raw Data	N/A				
Test Article Inventory	N/A				
BIO Batch Size	✓				
Assay of active content drug	N/A				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	~~✓~~	✓			
Biostudy lot numbers	N/A				
Statistics	N/A				
Summary results provided by the firm indicate studies pass BE criteria	N/A				
Waiver requests for other strengths / supporting data	N/A				

Additional comments: This is a waiver request for in vivo studies.

(I) The in vitro studies conducted, include ① Priming, Re-priming, spray content uniformity, ② spray pattern ③ Droplet Size Distribution using laser diffraction (including graphs for %transmission vs. time plots) and using cascade Impaction ④ Plume Geometry. In addition, composition of the test product, drawing of the test pump, and comparison of the metering device between the test and the reference products, are also included in this submission.

(II) However the test formulation is not Q & Q with RLD. and data diskette

Recommendation: **COMPLETE / INCOMPLETE** 6/10/2002

Reviewed by

Lin Whei Chuang Date 6/10/02

Revised 6/7/2000

ANDA 76-396

JUN 11 2002

Apotex Corp.
U.S. Agent for Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated April 8, 2002, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Calcitonin-Salmon Nasal Spray, 200 IU/spray.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You have failed to provide information to demonstrate that the proposed product is qualitatively and quantitatively the same as the reference listed drug product.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide the following:

> Please provide blank packaging records for your proposed production batch.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Emily Thomas
Project Manager
(301) 827-5862

Sincerely yours,

Gregory S. Davis for

Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-396
cc: DUP/Jacket
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/PRickman
HFD-615/MBennett
Endorsement:
HFD-615/GDavis, Chief, RSB Gregory S. Davis 11-JUN-2002 date
HFD-615/EThomas, CSO Emily Thomas 6/10/02 date
Word Document V:\Firmsnz\novex\ltrs&rev\76396.rtf
F/T EEH 06/10/02
ANDA Refuse to File!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-396 **FIRM NAME** Novex Pharma

RELATED APPLICATION(S) N/A **FIRST GENERIC?** Yes

DRUG NAME: Calcitonin, Salmon **DOSAGE FORM** Nasal Spray, 200 IU /Spray

Electronic Submission NA E-mail notification sent NA

Random Asgn Queue Random 5 Chem Team Leader Liu, Shing PM:

Labeling Reviewer MDO Micro Review NA PD study -Med Ofcr- NA

ACCEPTABLE

Letter Date April 8, 2002 **Received Date** April 11, 2002	
Comments EC 1 Yes **On Cards** Yes **Therapeutic Code** 3020400 Bone/Calcium-Phosphorous Metabolism	✓
Methods Validation Package (3 copies) Yes (Required for Non-USP drugs)	✓
Archival, and Review copies Field Copy Certification (Original Signature) Yes ✓ p1179	✓
Cover Letter Yes	✓
Table of Contents Yes	✓

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX	✓
Sec. II	**Basis for Submission** **NDA:** 20-313 RLD Miacalcin Firm: Novartis ANDA suitability petition required?____ If yes, consult needed for pediatric study requirement.	✓
Sec. III	**Patent Certification** Notes: 1. Paragraph: III 2. Expiration of Patent March 31. 2015 A. Pediatric Exclusivity Submitted?____ B. Pediatric Exclusivity Tracking System checked?____ **Exclusivity Statement** Yes	✓ ✓
Notes:		

Marcy Macdonald
847-573-9999 x 223

ACCEPTABLE

Sec. IV — Comparison between Generic Drug and RLD-505(j)(2)(A)

1. Conditions of use ✓
2. Active ingredients ✓ 4. Dosage Form ✓
3. Route of administration ✓ 5. Strength ✓

Sec. V — Labeling

1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ Notes:
2. 1 RLD label and I RLD container label ✓
3. 1 side by side labeling comparison with all differences annotated and explained ✓

Sec. VI — Bioavailability/Bioequivalence

Notes:

1. Financial certification (Form FDA 3454) — and Disclosure statement (Form 3455) — (for BE studies only!)
2. In Vivo Study Protocol(s) —
3. In Vivo Study(ies) —
4. Computer Disk Submitted Yes 1.1 in bio section blue and orange
5. Request for Waiver of In Vivo Study(les) Yes ✓ p57
6. In Vitro Dissolution Data —
7. Formulation Data Same? (Comparison of all Strengths) —
   (Opthalmics, Otics, Extemals, Parenterals)
8. Paragraph IV bio study acceptable for filing —
9. Lot numbers of products used in Bio-study —
10. DSI inspection request needed? —

1st Generic ____ 1st study for site ____ Other ____

E-mail notification to Bio PMs sent —

Sec. VII — Components and Composition Statements

Notes:

1. Unit composition and batch formulation
2. Inactive ingredients as appropriate X

Sec. VIII — Raw Materials Controls

Notes:

1. **Active Ingredients**
   a. Addresses of bulk manufacturers ✓
   b. Type 11 DMF authorization letters or synthesis ✓ p505
   c. COA(s) specifications and test results from drug substance mfgr(s) ✓
   d. Applicant certificate of analysis ✓
   e. Testing specifications and data from drug product manufacturer(s) ✓
   f. Spectra and chromatograms for reference standards and test samples ✓
   g. CFN numbers ____
2. **Inactive Ingredients**
   a. Source of inactive ingredients identified ✓
   b. Testing specifications (including identification and characterization) ✓
   c. Suppliers' COA (specifications and test results) ✓
   d. Applicant certificate of analysis ✓

Lot # 1X200.

(b) (4) [redacted]

ACCEPTABLE

Sec. IX	**Description of Manufacturing Facility** Notes: 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification Yes ✓ p 568 3. CFN numbers	✓
Sec. X	**Outside Firms Including Contract Testing Laboratories** Notes: 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers	✓
Sec. XI	**Manufacturing and Processing Instructions** Notes: 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than I Ox pilot batch) with Equipment Specified ✓ 3.If sterile product: Aseptic fill —/ Terminal sterilization — 4.1711ter validation (if aseptic fill) — 5. Reprocessing Statement ✓ p 617	✓
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ Notes: 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ Notes: 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address ✓	✓
Sec. XIV	**Controls for the Finished Dosage Form** Notes: 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓ p 755	✓
Sec. XV	**Stability of Finished Dosage Form** Notes: 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	✓

ACCEPTABLE

Sec. XVI	Samples - Statement of Availability and identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓ Notes:
Sec. XVII	**Environmental Impact Analysis Statement** ✓ p1167
Sec. XVIII	GDEA **(Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) ✓ p170 2. Debarment Certification (original signature) Yes ✓ 3. List of Convictions statement (original signature) ✓

Reviewing CSO/CST Emily Thomas

Date 6/6/02

✓ as of 9/16/02
Recommendation:

☐ FILE ☒ REFUSE to RECEIVE

Supervisory Concurrence: [signature] 11-JUN-2002 Date:

Duplicate copy sent to bio: _____ (Hold if RF and send when acceptable)

Duplicate copy to HFD-_____ for consult of type: _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

* NaCl is off - [redacted] (b) (4) ✓
✓ on benzalkonium chloride ✓
✓ on [redacted] (b) (4) - [redacted] (b) (4)
* No blank packaging records for scale up. ✓

Form Revised 11/30/2001

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

505(j)(2)(A) OK
16-SEP-2002
Copy Sent
* w/ additional info submitted in 9/12/02
NC

July 15, 2002

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

RESPONSE TO
REFUSAL TO FILE LETTER

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, of Ontario Canada is hereby forwarding in duplicate the response to the FDA Refusal to File Letter dated June 11, 2002. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
JUL 17 2002
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

July 12, 2002

Mr. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD U.S.A. 20857

Dear Mr. Rickman:

Re: RESPONSE TO REFUSAL TO FILE LETTER
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA #76-396

Further to your Refusal to File Letter dated June 11, 2002, we are pleased to provide you with our responses in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of the Refusal to File Notice as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included in Attachment No. 3.

1) *You have failed to provide information to demonstrate that the proposed product is qualitatively and quantitatively the same as the reference listed drug product.*

Response: Novex Pharma provided a side-by-side comparison table of Novex Pharma's formulation data with that of the Reference Listed Drug (RLD) on page 499 of the ANDA. The Novex Pharma formulation is based on the ingredients listed on the RLD label and is, therefore, qualitatively and quantitatively identical. Both products contain 2,200,000 IU/L of calcitonin-salmon as an active ingredient, (b) (4) of sodium chloride as an (b) (4) (b) (4), and (b) (4) of benzalkonium chloride (BAC) as a (b) (4). In the side-by-side comparison of formulation table, it was indicated that the Novex product contains (b) (4) (b) (4) of BAC because a (b) (4) BAC solution is used as the raw material; therefore, (b) (4) the amount is required to achieve the same final concentration of BAC as the RLD.

The pH of Novex Pharma's product is adjusted to (b) (4) with hydrochloric acid, which is the normal ingredient used to bring the pH of the formulation down to the desired range.

.../cont'd

However, due to the fact that [redacted] (b) (4)

Novex Pharma will comply with the decision.

[redacted] (b) (4). Our finding is further supported by the fact that the Canadian version of the RLD has a similar packaging system as the Novex Pharma product; the bottle is directly closed with a spray pump and no [redacted] (b) (4) is used. Stability data for the submitted batch (Lot No. 1X200 - 9 months) has been provided in Attachment No. 4 to show that the product is stable without the [redacted] (b) (4)

Based on the above facts, we conclude that our formulation is identical to the RLD.

2) *In addition, please provide blank packaging records for your proposed production batch.*

Response: Blank packaging records for the proposed production batch have been provided in Attachment 5.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Your sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC:mt
Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

September 11, 2002

Ms. Emily Thomas
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms.Thomas:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA #76-396

Further to your telephone conversation with Marcy Macdonald of Apotex Corp. on September 04, 2002, we are pleased to provide you with our responses to the requests put forth, in triplicate (Archival, Field and Review copies). For ease of review, we have prepared our responses in a question-and-answer format. An Application Form (FDA 356h) has been included as Attachment No. 1. A Field Copy Certification is included as Attachment No. 2.

1) *The formulation for Calcitonin-Salmon Nasal Spray, 200 IU/Spray is not Q1/Q2 equivalent due to the presence of* (b) (4) *. The innovator product does not contain* (b) (4) .

Response: Novex Pharma had included (b) (4) in the formulation as a (b) (4) (b) (4) was never used in the submitted batch, Lot No. 1X200.

Novex Pharma will revise the formulation to remove the (b) (4) . A revised composition statement is included in Attachment No. 3. Attachment No. 4 contains a Statement of Commitment to revise all appropriate documents including the Master Formula, product labeling and stability protocol, to reflect the removal of (b) (4) (b) (4) from the formulation. The revised documents will be submitted to FDA with our first amendment

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

for Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:mt

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

September 12, 2002

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, is hereby forwarding in duplicate the response to your requests furthering a telephone conversation with Marcy Macdonald on September 04, 2002. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
SEP 13 2002
OGD / CDER

2009-748

ANDA 76-396

SEP 16 2002

Apotex Corp.
U.S. Agent for Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the "Refuse to Receive" letter dated June 11, 2002 and your amendment dated July 15, 2002.

Reference is also made to the telephone conversation dated September 4, 2002 and your correspondence dated September 12, 2002.

NAME OF DRUG: Calcitonin-Salmon Nasal Spray, 200 IU/spray

DATE OF APPLICATION: April 8, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 17, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 76396/000
Stamp: 11-APR-2002
Regulatory Due:
Applicant: NOVEX
L4C 5H2
RICHMOND HILL, ONTARIO, CA
Priority:
Org Code: 600

Action Goal:
District Goal: 11-MAR-2003
Brand Name:
Estab. Name: CALCITONIN-SALMON
Generic Name:

Dosage Form: (SPRAY)
Strength: 200IU/SPRAY

Application Comment:

FDA Contacts: W. PAMPHILE (HFD-615) , Project Manager
S. LIU (HFD-623) 301-827-5848 , Team Leader

Overall Recommendation: ---

Establishment: CFN 9615251 FEI 3001617666
NOVEX PHARMA
L4C5H2
RICHMOND HILL, ONTARIO, , CA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: ADM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-SEP-2002				THOMASEM

Establishment: CFN (b) (4) (b) (4) FEI (b) (4)

DMF No: (b) (4) AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-SEP-2002				THOMASEM

Establishment: CFN (b) (4) (b) (4) FEI (b) (4)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

[redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-SEP-2002				THOMASEM

Establishment: CFN [redacted] FEI [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: I HAVE A DIFFERENT NAME FOR THE COMPANY IN THE APPLICATION:
[redacted]
(on 16-SEP-2002 by E. THOMAS (HFD-615) 301-827-5862)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-SEP-2002				THOMASEM

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

September 20, 2002

Ms. Emily Thomas
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms.Thomas:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA #76-396

Further to your telephone conversation with Marcy Macdonald of Apotex Corp. on September 16, 2002, we are pleased to provide you with our responses to the requests put forth, in triplicate (Archival, Field and Review copies). For ease of review, we have prepared our responses in a question-and-answer format. An Application Form (FDA 356h) has been included as Attachment No. 1. A Field Copy Certification is included as Attachment No. 2.

1) Please clarify the name and address of the active raw material manufacturer (b) (4) *This name does not match either of the two facilities located in* (b) (4) *that are listed in the FDA's ERS database.*

Response: We have confirmed with the active raw material manufacturer that the name and address are as presented in the ANDA as follows:

(b) (4)

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:mt

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

ORIG AMENDMENT
N/AC

September 23, 2002

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, is hereby forwarding in duplicate the response to telephone conversation with Marcy Macdonald on September 16, 2002. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
SEP 25 2002
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

NAT. - P III
10/3/02
for -569 P.M.P. to P IV -565

September 24, 2002

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

Re: REVISED PATENT CERTIFICATION for
Calcitonon-Salmon Nasal Spray, 200 IU/ Spray, ANDA No. 76-396

Further to our Abbreviated New Drug Application (ANDA No. 76-396) dated April 05, 2002 and in accordance with 21 CFR 314.94(a)(12)(viii), please find enclosed a revised Patent Certification for U.S. Patent Nos. 5,733,569 and 5,759,565. The originally submitted Paragraph III Certification is being revised to a Paragraph IV Certification at this time. In addition, please find enclosed, a statement in accordance with 21 CFR 314.95(b) and (d) certifying that Notice of Certification of Invalidity or Non-infringement of Patent has been provided to Novartis Corp., the holder of the approved application for MIACALCIN® Nasal Spray, 200 IU/dose and assignee of Patent Nos. 5,733,569 and 5,759,565. We are pleased to provide you with our responses in triplicate (Archival, Field and Review copies).

The revised Paragraph IV Patent Certification and a statement certifying that the application and patent holder has been provided with Notice of Certification of Invalidity or Non-infringement of Patent can be found in Attachment 3. A copy of the actual Notice of Certification of Invalidity or Non-infringement of Patent can be found in Attachment 4.

Should you require any further information, or have any questions or comments regarding the enclosed, please no not hesitate to contact me directly at (905) 508-2562 or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:mt

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

NEW CORRESP
NC

September 25, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

REVISED PATENT CERITIFICATION

RE: ANDA No. 76-396
Calcitonon-Salmon Nasal Spray
200 IU/ Spray
(5,733,569 and 5,759,565)

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Canada is forwarding the revised patent information regarding the above reference product.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

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OCT 0 3 2002
OGD / CDER

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

November 18, 2002

Office of Generic Drugs
CDER, FDA
MPNII, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT NEW CORRESP
NC

Re: Calcitonin-Salmon Nasal Spray,
200 IU/spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Canada, hereby submits Notice of Litigation pursuant further to our letter dated September 24, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

November 22, 2002

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FDA 356H FORM FOR
PATENT AMENDMENT

RE: Calcitonon-Salmon Nasal Spray
200 IU/ Spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Canada is forwarding in duplicate a FDA 356h Form regarding to the patent amendment sent November 18, 2002 for the above reference product.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

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2.1 - Pradhan, S.

Pamphile, Wanda
From: Sanchez, Aida L
Sent: Wednesday, January 08, 2003 1:01 PM
To: Pamphile, Wanda; Mazzella, Steven; Sigler, Aaron
Cc: Conner, Dale P; Huang, Yih Chain; Singh, Gur J P; Nerurkar, Shriniwas G; Pradhan, Sikta
Subject: RE: (b) (4) ANDA 76-396

Wanda:

Sorry for the delay, but I was on leave until yesterday. Bio's position on this issue is that if the chemist needs the inspection to ensure that the biobatch is acceptable, then we probably need the inspection. If the chemist is satisfied that the biobatch is acceptable without the inspection, then we do not need to inspect. We rely on the chemist to assure us that there are no problems with the biobatch used to demonstrate bioequivalence. Therefore, the chemist input on this issue is essential.

We will not need any additional bio testing if the only change is the supplier of the active ingredient. We mean by this that the formulation is the same, the device for the nasal spray has not changed, the manufacturing process and procedures are the same, and the site the product is assembled and finished is the same. This only applies if the only site change is the supplier of the active ingredient. If there are any other changes, please let us know. Thanks,

Lizzie

-----Original Message-----
From: Pamphile, Wanda
Sent: Thursday, January 02, 2003 5:11 PM
To: Sanchez, Aida L; Mazzella, Steven; Sigler, Aaron
Subject: FW: (b) (4) ANDA 76-396

Happy New Year to each of you.

Please look over this e-mail and comment on bio's position.

Thank you and have a nice day!

Wanda

-----Original Message-----
From: Dietrick, John M
Sent: Thursday, December 19, 2002 3:02 PM
To: Pamphile, Wanda
Cc: Adams, Linda A
Subject: (b) (4) ANDA 76-396

DFI attempted to schedule the PAI inspection at (b) (4) (b) (4) for ANDA 76-396 for (b) (4)

(b) (4) advised us that they are closing the (b) (4) facility at the end of the year. Although three batches of Calcitonin API were manufactured there for the sponsor, Novex, no commercial batches will be made there. Commercial batches of Calcitonin will be manufactured at (b) (4) facility in (b) (4) The sponsor will submit a supplement or amendment for this change. The (b) (4) facility was inspected in (b) (4) for another API and was acceptable. (b) (4) intends to manufacture three comparison batches in (b) (4) during (b) (4) and present the information to Novex. They do not expect to be finished and ready for any commercial batches until (b) (4) Manufacturing and testing records for the Calcitonin manufactured in (b) (4) will be transferred to the (b) (4) facility when the (b) (4) facility is closed.

I told the firm that I did not see any reason to inspect the old [redacted] (b) (4) facility and that I planned to cancel the inspection request. I stated that we may wish to inspect the [redacted] (b) (4) facility when they begin manufacture of calcitonin, but that I would advise the review division before we cancelled. [redacted] (b) (4) advised me that Novex was in no hurry for approval of the ANDA because of patent issues. Is cancelling ok with the review division? The firm would be rescheduled (at [redacted] (b) (4) only when a supplement or amendment is submitted to change sites of the API supplier.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 28, 2003

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

PATENT AMENDMENT

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
ANDA No.: 76-396
U.S. Patent No.'s: 5,733,569 and 5,759,565

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is submitting proof of patent notification to the patent holder regarding the above referenced patents and product.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

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APR 0 2 2003
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NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

April 23, 2003

ORIG AMENDMENT
N | AF
FPL

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs - HFD-600,
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
APR 24 2003
OGD / CDER

Dear Mr Rickman:

Re: LABELING AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray
ANDA No. 76-396

Further to your Labeling Deficiencies letter received at Apotex Corp on March 17, 2003, we are pleased to provide you with our responses in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h has been prepared and is enclosed as Attachment No. 2.

1. *CONTAINER (2 mL bottle):*

   Assure that the established name and strength appear as the most prominent information.

   Response: The format of the container (bottle) label has been modified in order to make the name and strength appear as the most prominent information. The bold has been removed from the left panel and the spacing between letters of the product name have been increased to improve prominence and legibility.

2. *CARTON (2 X 2 mL bottles):*

   a. *Revise the inactive ingredients section to reflect the removal of* (b) (4) *from the formulation.*

      Response: The inactive ingredients section of the carton has been revised to reflect the removal of (b) (4) from the formulation.

.../cont'd

b. We encourage you to include the product name and strength on the top panel.

Response: We regret that we are unable to include the product name and strength on the top panel due to standardized placement of the 128C bar code and unvarnished area for lot number and expiry date on the top flap of cartons. This allows our (b) (4) camera to check each article of finished product for the correct information. This standard top flap format does not provide room to accomodate placement of the product name and strength.

3. INSERT

a. DESCRIPTION
Revise the inactive ingredients section to reflect the removal of (b) (4) *from the formulation.*

Response: The Description section of the Insert has been revised to reflect the removal of (b) (4) from the formulation.

b. WARNINGS, Allergic Reactions subsection
Revise the second paragraph to read:

(b) (4)

Response: The second paragraph of the WARNINGS, Allergenic Reaction subsection of the Insert has been revised as requested.

4. PATIENT INSTRUCTIONS

a. TITLE
Add "One Spray, Once a Day" as the third line.

Response: As requested, the phrase "One Spray, Once A Day" has been added to the third line of the Title in Patient Instructions.

b. What is the Correct Dose of Calcitonin-Salmon Nasal Spray?
The innovator offers a Patient Education Program, as mentioned in the "How to Assemble and Use" labeling. In accordance with 21 CFR 314.94(a)(B)(iii), you are required to offer a similar program. Please comment.

Response: As per a telephone conversation with Ruby Wu of FDA on Monday April 14, 2003, verbal confirmation that Novex Pharma is not required to implement a Patient Education Program was provided. Ms. Wu (Division of Labeling and Program Support) advised Novex Pharma that after discussing the issue with her Team Leader at Labeling Division and in consultation with the Division of New Drugs, Novex Pharma will not be required to have a Patient Education Program similar to the Innovator's.

.../cont'd

5. *INFORMATION FOR THE PATIENT*

a. *What is osteoporosis after menopause? What causes it?*
Fourth paragraph, fourth sentence...revise to read "...medication, like calcitonin-salmon nasal spray, to..." [insert comma after "spray"]

Response: As requested, the fourth sentence of the fourth paragraph under the heading "What is osteoporosis after menopause? What causes it?" has been revised to include a comma after the word "spray".

b. *How does calcitonin-salmon nasal spray work?*
Second paragraph-revise "osteclasts" to read "osteoclasts"

Response: The second paragraph under the heading "How does calcitonin-salmon nasal spray work?" has been revised to correct the mispelling of "osteclasts" to "osteoclasts".

Please revise your labels and labelling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 50 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Response: As requested, the labels and labeling have been revised as instructed above. Twelve (12) printers proofs of the labeling for the bottle, carton and insert have been provided in Attachment No. 4. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the printer's proofs provided are a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, Novex Pharma will notify the agency, as necessary.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address: http://www.fda.gov/cder/cdernew/listserv.

Response: Novex Pharma acknowledges that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

As requested and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of Novex Pharma's final printed bottle label, carton label and insert provided in this Amendment with those provided in our original ANDA with all differences annotated and explained, has been provided in Attachment No. 3.

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:ia

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

June 05, 2003

Dr. Aaron Sigler
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Sigler:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

Further to your telephone conversation with Mike Lisjak of Apotex Corp. on June 04, 2003, we are pleased to provide you with our response to the request put forth, in duplicate (Archival and Review copies). For ease of review, we have prepared our response in a question-and-answer format. An Application Form (FDA 356h) has been included as Attachment No. 1.

1) *On page 499, the formulation data table comparing your proposed product to the RLD, you do not give a unit for the benzalkonium chloride, you simply state* (b) (4) *. Please update this page to include the unit.*

Response: As per your request, we have updated page 499 to include units for Benzalkonium Chloride Solution NF/EP (b) (4) . The revised page is included in Attachment No. 2.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

fc. Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:cd

Encl.

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

ORIG AMENDMENT BIOAVAILABILITY

N/AB

June 9, 2003

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Calcitonin-Salmon Nasal Spray
200 IU/spray
ANDA No. 76-396

To Whom It May Concern:

Apotex Corp. as the U.S. Agent for Novex Pharma, is hereby forwarding in duplicate the response to the telephone conversation with Mike Lisjak and Dr. Aaron Sigler of OGD, FDA on June 04,2003.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 847-279-7740

RECEIVED
JUN 10 2003
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

February 25, 2004

CBE AMENDMENT

Ms. Wanda Pamphile
Project Manager
Office of Generic Drugs, CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Pamphile:

Re: MINOR AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

Further to your Minor Amendment letter dated January 3, 2003, we are pleased to provide you with our responses in triplicate (Archival, Review and Field). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2, and a Field Copy Certification can be found in Attachment No. 3.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

Following this page, 14 pages withheld in full (b)(4)-CCI/TS

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FEB 27 2004
OGD/CDER

.../cont'd

17. (b) (4)

18.

B. *In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:*

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

Response: Novex Pharma acknowledges that evaluations for all facilities referenced in our ANDA have been requested from the Office of Compliance.

In addition, we would like to propose three additional contract testing facilities as described in the following table.

Facility Name and Address	Testing Functions
(b) (4)	Acceptance testing for release purposes of the active drug substance
	Acceptance testing for release purposes of excipients
	Acceptance testing for release purposes of compendial excipients

…/cont'd

In support of these additional facilities we have included cGMP certificates from these facilities in Attachment No. 35.

2. *Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.*

Response: We hereby acknowledge that any deficiencies regarding our bio-equivalence information will be communicated separately.

3. *Your labeling information is pending review. Deficiencies, if any, will be communicated separately.*

Response: Since this Minor Amendment letter was received on January 3, 2003, Novex Pharma has received a Labeling Amendment letter dated March 23, 2003 and responses to this request were submitted on April 23, 2003. Since the latter date, we have made minor changes to our labeling and have submitted 12 copies for review in Attachment No. 37. A side-by-side comparison of the labeling submitted in our April 2003 Labeling Amendment and the labeling submitted in this amendment is included in Attachment No. 36.

4. *We require an acceptable Methods Validation to support the ANDA and will schedule the study after the test method issues are resolved. Please provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approve prior to its completion.*

Response: Novex Pharma hereby commits to expeditiously resolve any deficiencies from the methods validation study if the ANDA is approved prior to its completion.

5. *Please provide any additional long term stability data that may be available.*

Response: 24 months shelf-life (refrigerated) stability data is included for review in Attachment No. 16 of this response.

6. *We acknowledge the submission of the Master Packaging Order in your amendment dated July 15, 2002. Please be advised that all packaging instructions should be included in the Master Formula.*

Response: Please be advised that it is our long-standing company policy to have separate manufacturing documents for (b) (4) and packaging operations.

.../cont'd

7. *DMF # (b) (4) for the (b) (4) is currently under review by another Division in the Center.*

Response: Novex Pharma hereby acknowledges that DMF No. (b) (4) is currently under reveiw.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2445, or FAX your requests to (905) 884-0357.

Yours sincerely,

Gina Sirianni, M.Sc.
Manager, US Regulatory Affairs

GS:kd

Encl.

Cai, Bing

From: Raw, Andre
Sent: Tuesday, March 09, 2004 9:17 AM
To: Cai, Bing; Liu, Shing Hou; Schwartz, Paul
Cc: Yu, Lawrence
Subject: Cacitonin

Hello

Attached is some information surrounding the review of a pending ANDA for Salmon Calcitonin Injection.
I should mention that not all issues in this application have been fully resolved so this is provided FYI only. Ultimately, we believe based upon both scientific criteria and past historical precedent, that ANDAs for Salmon Calcitonin peptide products can be approved without the requirement for additional clinical studies (e.g. antigenicity). This of course is based on the assumption that all CMC and Bio issues are fully resolved.

However, I want to clarify some points. (b) (4)

However, from my brief discussion with Bing Cai it appears that because the nasal solution is Q&Q to the innovator, that such studies will not be necessary.

The only common issue between the Injectable and the Nasal applications will likely relate to impurities. In the case of (b) (4) ANDA we are requesting additional information from the applicant to be absolutely certain that the impurity profiles are not dramatically different, particularly those above the (b) (4) level. This may become an issue with the nasal formulation as well.

I hope you find this information helpful. If there are any questions please let me know.

Thanks
Andre

(b) (4)0700.doc (1 MB) Memorandum.doc (44 KB) Deficiency-1.doc (28 KB) White_paper_12.doc (128 KB)

RECORD OF TELEPHONE CONVERSATION

Reference is made to T-con request dated February 11, 2004 (see attachment).

Firm: Do we need a new batch of the final product using the newly processed raw materials?

FDA: We will need 1 batch with 3 months of accelerated stability data. We will also need a commitment for 24 months of stability data. We will need the accelerated stability data prior to approval of the application because we want to see the impurity profile. Please submit a comparison of your drug product using the new raw materials and the reference dug product. Please feel free to include the original ANDA batch for comparison purposes. We want to compare the impurity profile mainly between the New product and the reference drug product. The agency is concerned about antigenicity for the drug product.

Firm: The new process is purer than the old batch.

FDA: You cannot use your old ANDA batch as justification for your new batch.

Firm: We agree to provide the stability information as requested by the agency.

DATE:
March 10, 2004

ANDA NUMBER:
76-396

PRODUCT NAME:
Calcitonin-Salmon Nasal Spray, 200 IU/spray

INITIATED BY:
Firm _X_ **Agency**__

FIRM NAME:
Novex Pharma

FIRM REPRESENTATIVE:
(b) (6)
Gina Sirianni
(b) (6)

TELEPHONE NUMBER:
905-884-2050 ext 2557

FDA REPRESENTATIVE:
Shing Liu, Ph.D.
Bing Cai, Ph.D.
Wanda Pamphile, Pharm.D.

SIGNATURE
Shing Liu S.H. Liu 3/11/04
Bing Cai 3/11/04
Wanda Pamphile 3/11/04

Orig: ANDA 76-396
Cc: Division File
Chem. I
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FAX TRANSMISSION

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario L4C 5H2
Tel: (905) 884-2050 Fax: (905) 884-9876

To:	Ms. Wanda Pamphile Project Manager, OGD, FDA	**Date:**	February 11, 2004
Fax #:	(301) 443-3839	**Pages:**	58 (including cover sheet)
From:	Gina Sirianni Manager, US Regulatory Affairs	**cc:**	Marcy Macdonald

Subject: **Teleconference Request – Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396**

Dear Ms. Pamphile:

It has been brought to our attention that the active raw material manufacturer of the above-referenced ANDA, [redacted] (b) (4) has modified their manufacturing process for Calcitonin (Salmon) EP. Specifically, the change involves [redacted] (b) (4) The active raw material manufacturer has recently filed with FDA an amendment to their DMF (No. [redacted] (b) (4)) to support this change. Novex Pharma would like to request a teleconference in order to discuss this change and its impact on our application currently under review with FDA.

The exhibit batch submitted in our ANDA was manufactured using raw material manufactured by the "old" process ([redacted] (b) (4) Lot No. 02116501 [Novex Pharma QC No. 5456]; however, we would like to propose that the change in manufacturing process be assessed as a minor change and all documentation supporting this change be submitted as a Minor Amendment to our ANDA. We also propose that a stability batch manufactured with "new-process" material is not required to support this change. Justification for this proposal is based on the manufacturer's demonstration of equivalence between the pre- and post-change material as described in the attached documents:

Drug Substance

1. Novex Pharma's comparison table of "old" and "new" raw material.
2. [redacted] (b) (4) comparison between the "old" and "new" production methods
3. [redacted] (b) (4) letter describing subsequent documents
4. [redacted] justification for consideration of the new process as a minor change
5. Batch data for pre- and post- change batches
6. Stability data – 9 months (old process)
7. Stability data – 4 weeks (new process)

---

8. Stability data – 1 month stress data (new process)

Please contact me at (905) 508-2445 in order to schedule the teleconference.

Yours sincerely,

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

ORIGINAL
XA

June 10, 2004

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Mr. Buehler:

Re: Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

There has been some restructuring within the Apotex Group of Companies to formally reflect that they are part of Apotex Inc. Effective immediately, the names of the various sites that make up the Apotex Group have changed.

Novex Pharma (a Division of Apotex Inc.) will now be named Apotex Inc. and will be distinguished from other locations by referring to it as the Richmond Hill Site.

A signed Application Form FDA 356h has been provided with this letter for the above-mentioned product. A complete listing of Novex Pharma's approved ANDAs and ANDAs currently under review by the Agency has been appended to this letter.

If you have any questions, please do not hesitate to contact me by phone at (905) 508-2396, by Fax at (905) 884-0357 or email at pbonnici@apotex.com.

Sincerely,
APOTEX INC. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

ORIGINAL

4-1

July 29, 2004

ORIG AMENDMENT
N/AB

Mr. Aaron Sigler
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

Further to your Bioequivalency Amendment letter dated March 30, 2004, we are pleased to provide you with our responses in duplicate (Archival [blue jacket] and Review [orange jacket]). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

1. *For Spray Pattern Analysis, the ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90 - 1.11 range. However, the ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was not within the acceptable 0.90 - 1.11 at both life sectors. The overall variability of the test product was more than that of the reference product. Hence, the Spray Pattern data are not acceptable. These data were analyzed in the DBE using the Population Bioequivalence method (as outlined in the June 1999 draft Nasal BA/BE guidance). The results of these analyses also demonstrate the lack of equivalence in spray patterns between the test and reference products. Please note that based on the April 2003 draft Nasal BA/BE Guidance, measures of Spray pattern, using automated Laser analyses, are Area and Ovality ratio. Measurement of Dmax and Dmin axes is not required for such analyses. You have the option of repeating Spray Pattern Testing using the conventional impaction technique (thin layer chromatography). If this technique is used, the Agency encourages you to use computerized image measurements to minimize potential bias.*

/cont'd

RECEIVED
JUL 30 2004
OGD / CDER

Response: As per the Agency's request, we have repeated the spray pattern analysis using a manual (TLC) technique, TM-1628, Issue No. 2, Spray Pattern Determination for Calcitonin Salmon Nasal Spray; please refer to Attachment No. 3 for a copy of this method. The resultant spray patterns were analyzed manually by the Center of Mass method as an automated instrument was not available for computerized image measurements. As per the April 2003 draft guidance, BA/BE Studies for Nasal Aerosols and Nasal Sprays For Local Action, Dmax and the Ovality ratio should be used for the statistical evaluation of BE for manual analyses. The T/R ratios for Dmax and Ovality are within the 0.9 - 1.11 range at distances of 3 cm and 6 cm from the actuator orifice and therefore, the test and reference products are equivalent in spray pattern. Please refer to Attachment No. 8 for the spray pattern data in SAS format on diskette. Attachment No. 4 includes the 20% representative spray pattern images.

2. *The data showed no drug deposition below the top stage of the cascade impactor. In the FDA's experience with the aqueous nasal sprays, low but measurable levels of drug are observed below the top stage of the impactor. The factors, which may improve deposition in the lower stage include (1) development and use of an assay with greater sensitivity and (2) the use of an atomizing chamber different from the USP throat recommended for oral inhalation products. The revised draft Nasal BA/BE guidance issued on April 2003 recommends the use of a 2L or larger flask. Hence, please repeat the test considering the recommendations made in the guidance. Please provide the detailed methodology of Cascade impaction (test, including the operating parameters).*

Response: Determination of drug in small particle size/ droplet by cascade impactor was repeated as recommended by the Agency. A 5 L flask was used instead of the conventional induction port and the resultant data indicate similar deposition below the top stages for the test product and Reference Listed Drug. Please refer to Attachment No. 8 for the Cascade Impaction data in SAS format on diskette, Attachment No. 5 for the parameters used for the Cascade Impactor (PD-113, Issue No. 2) and Attachment No. 6 for the Operation of the Automated Spray Pump Actuation System (GM-143, Issue No. 7).

3. *The in vitro testing conducted on plume geometry is deficient. SOP for Plume Geometry measurements should be provided. The test/ref ratios of the geometric means for plume angles are within the acceptable limits of 0.9 - 1.11. However, the width measurements are not acceptable, because they do not appear to represent the observed width of the plume. Furthermore, it is not clear if all measurement were made at the same distance from the orifice.*

Based on the submitted data, the T/R ratio of geometric means of spray width (based on plume geometry) were in the range of 1.03 - 1.07. These data suggest that the width of the test product spray is similar to that of the reference product.

.../cont'd

On the other hand, T/R ratios for Dmax (based on spray pattern) were in the range of 1.22 - 1.29, which indicates that the width of the test product spray pattern is considerably greater than that of the reference product. Please explain these results, given that the same technique ([(b) (4)]) was used for both plume geometry and spray pattern analyses.

To impart objectivity to the width measurements, the width should be measured at a fixed distance from the actuator orifice. As recommended in April 2003 draft Nasal BA/BE guidance, the width should be measured at the greatest distance chosen for the spray pattern analysis (5 cm for the present study). Plume geometry SOP should provide detailed methodology, including the criteria employed for defining the limits of the spray width.

Response: Plume geometry analysis was repeated and the data demonstrate a ratio of geometric means for plume angle and plume width within the acceptable limits of 0.9 to 1.11. The plume angle and plume width were determined visually from a single snapshot taken in the fully formed region of the spray (80 msec). The gradient palette in the [(b) (4)] software was used for analysis. The plume angle measurements were made at the orifice of the actuator tip and the plume width measurements were made at a vertical distance of 6 cm from the actuator tip orifice. The distance represents the greatest distance selected for the spray pattern analysis. The plume geometry data in SAS format are included on diskette in Attachment No. 8. The 20% representative plume geometry images are included on diskette for review in Attachment No. 8. The test method used for the plume geometry measurements is provided in Attachment No. 7 (PD-103, Issue No.3).

The reason the T/R ratio for Dmax based on the spray pattern analysis was greater than the T/R ratio for plume width based on plume geometry analysis, given that the same [(b) (4)] characterization system was used, may be due to the difference in the analysis technique. First, spray pattern is determined by averaging the images of the entire spray whereas the plume geometry is determined from a single snapshot at a delay time in the fully formed plume region. The software compensates for the background noise when images are averaged but does not compensate for background noise when analysing a single frame.

Second, the plume width was not measured at the greatest vertical distance chosen from the spray pattern analysis (i.e. 5 cm for the initial submission). In the original submission, the width was determined at a vertical distance where the spray particles were intense. This distance was closer to the orifice of the actuator tip (i.e. 2 to 3 cm). The width measurement itself was determined based on the outer edges of the more intense particle region (i.e. intensity profile window indicated a minimum 50 % intensity) rather than on the outer edges of the actual plume (i.e. intensity profile window indicates a minimum 5 to 10 % intensity).

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2445, or FAX your requests to (905) 884-0357.

Yours sincerely,
APOTEX INC. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:kd

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

July 29, 2004

ORIG AMENDMENT
N/AF

Ruby Wu
Office of Generic Drugs, CDER, FDA,
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

Re: LABELING AMENDMENT – Calcitonin-Salmon Nasal Spray, 200 IU/Spray
Response to Notice of Labeling Deficiency, ANDA No. 76-396

Further to your Notice of Deficiencies letter dated June 03, 2004, we are pleased to provide you with our responses in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h has been prepared and is enclosed as Attachment No. 2.

Labeling Deficiencies:

1. *CONTAINER (2 mL bottle):*
   If space permits, we encourage you to add "14 Dose Bottle".

   Response: Due to the limited size of the bottle label we are unable to include"14 Dose Bottle" on the main panel. However, we were able to include a phrase of similar effect on the side panel as narrative text: "This bottle contains at least 14 doses". This is similar to the phrase "Each bottle contains at least 14 doses" found on the carton side panel. Twelve (12) copies of the revised labeling are included for review in Attachment No. 5.

2. *CARTON (2 x 2 mL bottles):*
   Main Panels – We encourage you to add "14 Doses Per Bottle".
   Side panel – "Store bottle in use at room temperature 20°-25°C (68°-77°F)
   [for up to 30 days]...second bottle in refrigerator at 2°-8°C (36°-46°F) until..."

.../cont'd

Response: The phrase "14 Doses Per Bottle" has been added to the front and back panels of the 2 x 2 mL carton. We have also revised the storage statement on the side panel as per the Agency's recommendations. Twelve (12) copies of the revised labeling are included for review in Attachment No. 5.

3. *INSERT*
   a. *WARNINGS, Allergic Reactions subsection*
   Revise the second paragraph to read:
   "For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of calcitonin-salmon injection. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the XXXX Department of Novex Pharma." Please revise the last sentence accordingly. A copy of the skin testing protocol is attached. Please submit, for our review and comment, a similar skin testing protocol that will be provided to practitioners who may request a copy of the protocol. Assure that the protocol will be available when your ANDA is approved.

   b. *PRECAUTIONS, Information for Patients, Seventh bullet: add as the last 2 sentence.*
   "You should keep track of the number of doses used from the bottle. ***After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.*** *"*

   c. *HOW SUPPLIED, Store and Dispense: "Store unopened bottle(s) in refrigerator between 2°-8°C (36°-46°F)...Stgore bottle in use at room temperature 20°-25°C (68°-77°F) in an ..."*

Response: We have revised the second paragraph of the *WARNINGS, Allergic Reactions* subsection of the insert to read as per the Agencies recommendations. The last sentence has been revised to " ... available from the Customer Service department of Apotex Corp. (1-800-4-APOTEX)". We have also drafted a skin testing protocol based on the one provided in the Agency's deficiency letter. The draft protocol is included in Attachment No. 3 for review. The protocol will be transferred to Apotex Corp.'s Quality Affairs department for distribution to physicians when requested via Apotex Corp.'s Customer Service department.

The *PRECAUTIONS, Information for Patients* and *HOW SUPPLIED, Store and Dispense* subsections of the insert has also been revised as per the Agency's recommendations. Twelve (12) copies of the revised labeling are included for review in Attachment No. 5.

.../cont'd

4. *PATIENT INSTRUCTIONS*
   a. *Important Facts About Your Medication*
      i. *Second bullet: "... at 2°-8°C (36°-46°F). Do not freeze"*
      ii *Third bullet: "...at room temperature, 20°-25°C (68°-77°F), in an..."*
   b. *How to use Calcitonin-Salmon Nasal Spray, Step 5, third sentence: "...at room temperature (20° - 25°C [68° - 77°F]) in the ..."*

   Response: The Patient's Instructions have been revised as per the Agency's recommendations. Twelve (12) copies of the revised labeling are included for review in Attachment No. 5.

5. *INFORMATION FOR THE PATIENT*
   a. *How do I use calcitonin-salmon nasal spray? Add as the last 2 sentence: "You should keep track of the number of doses used from the bottle.* ***After 14 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty."***
   b. *Possible Side Effects, Bullet one: "Nasal symptoms such ..." [delete comma]*

   Response: The Information for the Patient section has been revised as per the Agency's recommendations. Twelve (12) copies of the revised labeling are included for review in Attachment No. 5.

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please be advised that in addition to the changes made to our labeling in response to the Agency's labeling comments we have also made a change to the "manufactured by" information on all labeling as our firm has recently undergone a name change from Novex Pharma to Apotex Inc. as described in a letter to FDA dated June 10, 2004. For ease of review, all changes to our product labeling are captured in the side-by-side labeling comparison included in Attachment No. 4 between our previously submitted product labeling (Minor Amendment dated February 25, 2004) and that provided in this Amendment.

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. – Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:dt

Encl.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 13, 2004

ORIG AMENDMENT

N/AB

Office of Generic Drugs (OGD) - HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

Re: RESUBMISSION OF ELECTRONIC FILES
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

Further to your fax dated August 09, 2004, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your fax as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

1. *CD-ROM includes non archival files. Please resubmit all electronic files.*

   Response: As requested, the electronic files for 20% Representative Plume Geometry Images have been resubmitted in an archival format (PDF). The file contains the same information that was previously sent on the CD included with the Bioequivalency Amendment dated July 29, 2004. The electronic (CD) file is enclosed in Attachment No. 3.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,
Apotex Inc. - Richmond Hill Site

Per: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

cc: Apotex Corp.

RECEIVED
AUG 16 2004
OGD/CDER

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/A/C

January 31, 2005

Ms. Wanda Pamphile
Project Manager
Office of Generic Drugs, CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Pamphile:

Re: MAJOR AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

Further to your Major Amendment letter dated July 29, 2004, we are pleased to provide you with our responses in triplicate (Archival, Review and Field). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2, and a Field Copy Certification can be found in Attachment No. 3. We are also providing a Bioequivalence "Desk" copy of this amendment containing the cover letter, attachment nos. 1-3 and 19-20, and one CD-ROM with bioequivalence files.

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. (b) (4)

Following this page, 4 pages withheld in full (b)(4)-CCI/TS

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Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

.../cont'd

Proudly Canadian

The following information is provided in support of this new batch.

Document Description	Attachment No.
(b) (4)	12
	13
	14
	15

(b) (4)

B. *In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:*

1. *Please respond to the bioequivalence deficiencies faxed on March 30, 2004.*

   Response: Our response to the bioequivalence deficiencies was submitted to the agency on August 13, 2004.

2. *Please respond to the labeling deficiencies faxed on June 3, 2004.*

   Response: Our response to the labeling deficiencies was submitted to the agency on July 29, 2004.

.../cont'd

3. *Please provide any stability data on the new exhibit batch that may be available.*

Response: Stability reports for the new exhibit batch of Calcitonin-Salmon Nasal Spray, 200 IU/mL, batch no. GN9039 are included in Attachment No. 14.

Additional Bottle Size - 3.7 mL Fill Volume (30 Actuations)

In addition, we would like to propose an additional package size of one 3.7 mL fill bottle (30 doses) per carton. In support of this additional pack size we have manufactured one batch of this new fill volume as described in the following table. The drug substance batch was manufactured at the (b) (4) facility.

Batch Description	Batch Number	Batch Size	Manufacture Date*	Date Tested*	Use of Batches	Drug Substance Batch No.
(b) (4)						

* Functions performed at Apotex Inc. - Richmond Hill site

The following table summarizes the information included in this Amendment in support of this additional pack size.

Supporting Data for Calcitonin-Salmon Nasal Spray, 200 IU/spray, 3.7 ml fill; Batch No. GP7145/GP7146	Attachment No.
Executed Production Documents • (b) (4) •	16
Drug Product Certificates of Analysis • (b) (4) •	17
Packaging component Certificates of Analysis • (b) (4) •	18

.../cont'd

Following this page, 1 page withheld in full (b)(4)

Please be advised of the following points with respect to this new batch:

- There is no change in the bulk Master Formula. Please be advised that this batch size indicates the use of [redacted] (b) (4), if necessary. [redacted] (b) (4) was not used [redacted] (b) (4) in the stability batch presented in this amendment. We had committed in the past to remove [redacted] (b) (4) from our labeling and Master Formula. However, inclusion of this [redacted] (b) (4) in the Master Formula was an oversight and will be removed from our commercial manufacturing documents.

- The new fill volume uses a different bottle (5 mL). The manufacturer is the same as that of the bottle used for the 2 mL product. Refer to the manufacturer's DMF for complete details.

- The new fill volume uses a different pump (longer dip tube). The manufacturer is the same as that of the pump used for the 2 mL product. A description of the materials of composition for the 3.7 mL pump is provided in Attachment No. 22. Materials of construction are identical for both pumps. The only differences between the 2 and 3.7 ml pumps are the physical dimensions of the dip tube. Refer to the manufacturer's DMF for complete details.

- New labelling for the new fill volume has been generated. Proposed labelling in pdf format is provided on compact diskette in Attachment No. 28 of the Review Copy only. The insert is also provided in Word format. Copies of the RLD labelling are provided in Attachment No. 26. An annotated side-by-side comparison of the proposed 3.7 mL labelling and the RLD labeling are provided in Attachment No. 27.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
M/AA

April 19, 2005

Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

Re: GRATUITOUS AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Calcitonin-Salmon Nasal Spray, 200 IU/spray. This Gratuitous Amendment has been provided in triplicate (Archival, Review and Field copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment No. 1, and a Field Copy Certification can be found as Attachment No. 2.

We would like to inform the Agency of the following changes made to the Master Formula for Calcitonin-Salmon Nasal Spray, 200 IU/spray:

-

..../cont'd

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- Removal of the [redacted] (b) (4) and the relevant steps in the manufacturing process as committed to in the amendments submitted on February 25, 2004 and January 31, 2005.

A copy of each of the revised Master Formulae for the [redacted] (b) (4) batch sizes are provided as Attachment No. 3.

In addition, we also would like to notify the Agency of changes to the Calcitonin Salmon Raw Material test method, Assay and Identification of Calcitonin (Salmon) and Determination of Related Peptides in Calcitonin (Salmon) Raw Material – TM-1085. The changes are as follows:

- [redacted] (b) (4)
-
-

A copy of the revised method is provided as Attachment No. 4.

We trust that the information submitted at this time is sufficient for review of this gratuitous amendment for Calcitonin-Salmon Nasal Spray, 200 IU/spray. Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:ml

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N | AF

May 18, 2005

Ruby Wu
Office of Generic Drugs, CDER, FDA,
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Wu:

Re: LABELING AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray, ANDA No. 76-396

Further to your Labeling Deficiencies letter dated May 10, 2005, we are pleased to provide you with our responses in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h has been prepared and is enclosed as Attachment No. 2.

Labeling Deficiencies:

1. *Container Labels (2 mL bottle [14 doses per bottle] and 3.7 mL bottle [30 doses per bottle]) Principal display panel: Add "14 dose bottle" to the 2 mL bottle and "30 dose bottle" to the 3.7 mL bottle.*

   Response: During the telephone conversation between yourself and Gina Sirianni, on May 16, 2005, it was agreed that the information "14 dose bottle" and "30 dose bottle" will not be added to the principal display panels of the 2 mL and 3.7 mL bottle labels, respectively. The rationale being that the bottle labels are too small to contain this information on the front panel. If this information were to be added it would have to go in the strength bar and this is not consistent with Apotex Inc. labeling format. In addition, this information is already provided on the side panel of the label. Therefore, the information will not be added to the main panel but rather it will be bolded on the side panel to make the text more prominent.

.../cont'd

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

2. *Carton (2 x 2 mL bottles and 1 x 3.7 mL bottle)*
2 x 2 mL bottle carton: Satisfactory as of the July 29, 2004 submission.

Response: We acknowledge that the 2 x 2 mL bottle carton submitted on July 29, 2004 is satisfactory.

1 x 3.7 mL bottle carton:
a. *"3.7 mL bottle": [add "bottle"]*

Response: Due to the limited space available on the label, we are unable to add "bottle" after "3.7 mL". There is an option to place "bottle" beneath "3.7 mL"; however in our opinion, this is not aesthetically pleasing, and not consistent with our labeling format for other nasal spray products. Therefore, as agreed in the telephone conversation between yourself and Gina Sirianni on May 16, 2005, the word "bottle" will not be added after "3.7 mL" due to esthetic reason and prior precedence set for our other nasal spray products, e.g. Desmopressin Acetate Nasal Solution, 0.01% (Nasal Spray), ANDA No. 76-703, approved on January 27, 2005, in which the word "bottle" was not included after the fill volume on the carton.

b. *Principal display panel: Increase the prominence of "30 Doses Per Bottle"*

Response: We have increased the font size of the statement "30 Doses Per Bottle" to make it more prominent.

3. *COMBINATION Profession Insert, Patient Instructions for Use and Patient Information*
2 mL bottle: Satisfactory as of the July 29, 2004 submission.
3.7 mL bottle: Satisfactory as of the January 31, 2005 submission.

Response: We acknowledge that the Combination Profession Insert, Patient Instructions for Use and Patient Information for both the 2 mL bottle and 3.7 mL bottle submitted on July 29, 2004 and January 31, 2005, respectively, are satisfactory.

4. *Skin Testing Protocol*
Satisfactory as of the July 29, 2004 submission.

Response: We acknowledge that the Skin Testing Protocol provided in the July 29, 2004 submission is satisfactory.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

.../cont'd

Response: An electronic copy of the labeling for the container labels (2 mL and 3.7 mL bottles) and carton (3.7 mL) have been provided in the Review copy only. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the electronic labeling provided are true representations of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, Apotex Inc. will notify the agency, as necessary.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Response: We acknowledge that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

BIOEQUIVALENCY AMENDMENT

ANDA 76-396

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG 1 6 2005

APPLICANT: Apotex Corp.
U.S. Agent for: Apotex Inc.

TEL: 847-279-7740

FAX: 847-353-2982

ATTN: Marcy MacDonald

FROM: Beth Fabian-Fritsch

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 29, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcitonin-Salmon Nasal Spray, 200 IU/spray.

Reference is also made to your amendment dated January 31, 2005.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY DEFICIENCIES

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray
2 mL Product and 3.7 mL Product

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The 3.7 mL product fails to meet recommendations for priming given in the CDER draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action." This guidance recommends: "For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-105 percent of label claim." It is noted that your 2 mL product met that recommendation.
2. Please indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, please provide the name of the manufacturer and the details of automated actuator settings.
3. Based on the Standard Operating Procedure (SOP) submitted, it is not clear what automated actuator parameters (settings) were used for the 2 mL fill size product, and if the settings were same for testing the test and reference products. Please provide this information.
4. The cascade impaction data for the 2 mL fill size product are incomplete because you did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance of the cascade impactor runs for the test and reference products. Please provide the requested information.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/AB

August 18, 2005

Ms. Beth Fabian-Fritsch
Project Manager, Division of Bioequivalence
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Fabian-Fritsch:

Re: BIOEQUIVALENCY AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Further to your Bioequivalency Amendment letter dated August 16, 2005, we are pleased to provide you with our response in duplicate, Archival (blue jacket) and Review (orange jacket) copies. For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

The following deficiencies have been identified:

1. *The 3.7 mL product fails to meet recommendations for priming given in the CDER draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action". This guidance recommends: "For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-105 percent of label claim." It is noted that your 2 mL product met that recommendation.*

   Response: The priming data for the 3.7 mL product that failed to meet the 95 – 105% limit as per the draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", was performed on 10 bottles. This test has been repeated on 30 bottles as recommended in the draft guidance. The geometric mean of the spray content uniformity results from the 30 bottles at the Beginning life stage (6^{th} spray) falls within 95 – 105% of label claim. Based on this data (Table 1), priming was established after the pump had been actuated five times.

.../cont'd

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Table 1:

Assay per Spray At Beginning Life Stage (Spray # 6) for Batch No. GP7146		
Bottle No.	**Weight (g)**	**Assay (%)**
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
Mean:		**96**
Min.:		(b) (4)
Max.:		

.../cont'd

2. *Please indicate if an automated actuator was used for determination of the Unit Spray contents. If an automated actuator was used, please provide the name of the manufacturer and the details of automated actuator settings.*

Response: An (b) (4) Automatic Spray Pump Actuation Station was used for the determination of Unit Spray contents for both the test and reference products. A copy of the test method GM- 143, which contains the details of the actuator settings, had been included in Attachment 21 of the Major Amendment dated January 31, 2005. The details of the settings are provided below for your convenience.

Actuator Settings of The (b) (4) Spray Pump Actuation Station for The Calcitonin Nasal Spray Pump ((b) (4))	
Parameters	**Settings**
Dose Time (msec)	20 ± 2
Return Time (msec)	30 ± 5
Hold Time (sec)	0.5
Actuation Force (kg)	6.0 ± 0.5

3. *Based on the Standard Operating Procedure (SOP) submited, it is not clear what automated actuator parameters (settings) were used for the 2 mL fill size product, and if the settings were same for testing the test and reference products. Please provide this information.*

Response: For the 2 mL fill size product, the same (b) (4) actuation station and settings, as described in the response to question 2 above, were used for both the test and reference products.

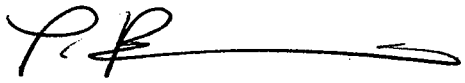
4. *The cascade impaction data for the 2 mL fill size product are incomplete because you did not provide information regarding (1) Units of the comparative data in Groups 1, 2 and 3, and (2) Data supporting mass balance of the cascade impactor runs for the test and reference products. Please provide the requested information.*

Response: Due to the limited capacity for text in SAS, the units of the comparative data in Group 1, 2 and 3 and the data supporting mass balance may not have been clearly identifiable. Please refer to the Table entitled "Summary of Droplet Size Distribution by Cascade Impactor for Calcitonin Salmon" provided as Attachment No. 3, which clearly provides the unit of measure (i.e. microgram/stage), as well as the mass balance data (described as "Material Balance"). Please note, the data provided in Attachment No. 3 is the same as that provided in SAS.

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 30, 2005

XA

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Mr. Buehler:

Re: US Agent Change -
Calcitonin-Salmon Nasal Spray, 200 IU/spray, ANDA No. 76-396

This letter serves to inform you that the US Agent for Apotex Inc.-Richmond Hill Site will be moving from their current office in Lincolnshire, Illinois to a new office in Weston, Florida, effective September 1, 2005.

The new contact information for our US Agent is as follows:

Name:	Kalpesh Shroff
Address:	Apotex Corp. 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326
Tel:	(954) 349-4217
Fax:	(954) 349-4233

We are submitting a copy of this letter to each Apotex Inc.-Richmond Hill Site ANDA currently under review with the Agency or approved by the Agency, however, a comprehensive list of all Apotex Inc.-Richmond Hill Site ANDAs is appended to this letter for your convenience. Please be reminded that on August 15, 2005 the Agency was notified of a transfer of ownership of Apotex Corp. products to Apotex Inc.-Richmond Hill Site. Accordingly, products formerly belonging to Apotex Corp. are also impacted by this change.

If you have any questions, please do not hesitate to contact me by phone at (905) 508-2396, by Fax at (905) 884-0357 or email at pbonnici@apotex.com.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs (Liquids)

PB:cd

Encl.

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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

September 01, 2005

Ms. Beth Fabian-Fritsch
Project Manager, Division of Bioequivalence
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Dear Ms. Fabian-Fritsch:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Further to your telephone call to Ms. Gina Sirianni of Apotex Inc. on August 30, 2005, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 1.

The following deficiencies have been identified:

1. *Provide a table containing the comparative data for cascade impaction for groups 1, 2 & 3 including the units.*

   Response: As requested, comparative data for cascade impaction for groups 1, 2, and 3 including the units is provided in Tables 1 and 2 of Attachment No. 2 for test and reference products, respectively.

.../cont'd

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2. *Explain how the mass balance data were derived from the raw data of cascade impaction for both test and reference.*

Response: The mass balance data in Tables 1 and 2 of Attachment No. 2 were derived by the following formula:

$$\text{Material Balance (\%)} = \frac{\text{Deposited Amount (µg)}}{\text{Actual Amount (µg)}}$$

The Deposited Amount is derived by HPLC analysis of samples collected as per sections 5.4.8 to 5.4.10 of test method PD-113, "Determination of Aerodynamic Particle Size Distribution in Calcitonin Salmon Nasal Spray Using (b) (4) Cascade Impactor and (b) (4) Automated Spray Pump Actuation Station", which was submitted as Attachment No. 5 in our Bioequivalency Amendment dated August 13, 2004.

The Actual Amount is calculated using the differences in weight of the samples before and after spraying, density of the product, and assay value of each lot (determined by test method TM-1056, which was submitted as Attachment No. 26 in our Minor Amendment dated February 25, 2004).

Please refer to the equations and sample calculations in Tables 1 and 2 of Attachment No. 2.

In accordance with the CDER draft Guidance for Industry, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", mass balance was based on drug deposition on each of induction port, the top stage, and all lower stages to the filter. Details of the test method can also be found in PD-113.

3. *Provide mass balance data for test and reference products.*

Response: Mass balance data for test and reference products is provided in Tables 1 and 2, respectively, of Attachment No. 2. Please note that the term "Material Balance" is used in place of "Mass Balance" in Tables 1 and 2.

.../cont'd

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,

for:

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:ac

Encl.

BIOEQUIVALENCE AMENDMENT

DEC 16 2005

ANDA 76-396

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corporation

TEL: 847-279-7748

ATTN: Kalpesh Shroff

FAX: 847-353-2982

FROM: Beth Fabian-Fritsch

PROJECT MANAGER: (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 18, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcitonin-Salmon Nasal Spray, 200 IU/spray, 2 mL and 3.7 mL.

Reference is also made to your amendment dated September 1, 2005.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

DEC 16 2005

BIOEQUIVALENCE DEFICIENCIES

ANDA: #76-396 APPLICANT: Novex Pharma

DRUG PRODUCT: Calcitonin-Salmon Nasal Spray, 200 IU/spray
2 mL Product and 3.7 mL fill sizes

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The in vitro performance data are incomplete because spray pattern ovality fails to meet the acceptance criteria due to high variability of the test product compared to the reference product.

It is noted that you have conducted manual quantitation of spray patterns. To reduce variability in measurements, you may repeat the spray pattern quantitation using an automated/computerized method measuring area and ovality ratios of spray pattern images. The revised data should be analyzed using the Population Bioequivalence Method employing $sigma_{T0}$ of 0.1 and epsilon of 0.01.

You also have the option of repeating the test using a non-impaction (laser-sheet) method. Equivalence of spray patterns of test and reference products by such methods is also based on the spray pattern area and ovality ratio data, based on the true pattern shapes. If the test is repeated, it should be performed on the same batches of the test and reference products, if the batches are still within the expiration date. If they have expired, the test should be performed using three new batches of the marketed test and the available reference products.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ORIGINAL

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

February 23, 2006

ORIG AMENDMENT
N | AF

Ruby Wu
Division of Labeling and Program Support
Office of Generic Drugs, HFD-610
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Wu:

Re: GRATUITOUS LABELING AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray, ANDA No. 76-396

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Labeling Amendment to our unapproved application for Calcitonin-Salmon Nasal Spray, 200 IU/Spray. This Gratuitous Labeling Amendment has been provided in duplicate (Archival and Review copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment 1.

This Gratuitous Labeling Amendment is submitted to update the labeling following a revision to the Reference Listed Drug labeling, Miacalcin® (calcitonin-salmon) Nasal Spray, manufactured by Novartis Pharmaceuticals Corp. Please note that no changes have been made to Apotex Inc.'s package insert other than those made on the RLD package insert. A copy of the Miacalcin® labeling has been provided in Attachment 2 for reference.

In accordance with 21 CFR 314.94 (a)(8)(iv), a side-by-side comparison of Apotex Inc.'s final package insert (prescribing information and patient instruction guide) provided in this Amendment for the 2 mL and 3.7 mL package sizes and that provided in our Labeling Amendment submitted on July 29, 2004 for the 2 mL package size and our Major Amendment submitted on January 31, 2005 for the 3.7 mL package size, with all differences annotated and explained have been provided in Attachment 3.

An electronic copy of the labeling has been provided with the Review copy only. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the enclosed labeling for the package insert is a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, Apotex Inc. will notify the agency, as necessary.

RECEIVED
FEB 24 2006
OGD/CDER

.../cont'd

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Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:ks

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
4/7/06

April 05, 2006

Ms. Beth Fabian-Fritsch
Project Manager, Division of Bioequivalence
Office of Generic Drugs (HFD-650)
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Fabian-Fritsch:

Re: BIOEQUIVALENCE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Further to your Bioequivalency Amendment letter dated December 16, 2005, we are pleased to provide you with our response in duplicate, Archival (blue jacket) and Review (orange jacket) copies. For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

The following deficiencies have been identified:

The in vitro performance data are incomplete because spray pattern ovality fails to meet the acceptance criteria due to high variability of the test product compared to the reference product.

It is noted that you have conducted manual quantitation of spray patterns. To reduce variability in measurements, you may repeat the spray pattern quantitation using an automated/computerized method measuring area and ovality ratios of spray pattern images. The revised data should be analyzed using the Population Bioequivalence Method employing sigma$_{TO}$ of 0.1 and epsilon of 0.01.

You also have the option of repeating the test using a non-impaction (laser-sheet) method. Equivalence of spray patterns of test and reference products by such methods is also based on the spray pattern area and ovality ratio data, based on the true pattern shapes. If the test is repeated, it should be performed on the same batches of the test and reference products, if the batches are still within the expiration date. If they have expired, the test should be performed using three new batches of the marketed test and the available reference products.

.../cont'd

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Response: We have repeated the spray pattern test using the impaction thin layer chromatographic method with manual analysis. The test was performed on three different batches of the reference product (Batch Nos.-Expiry Date: H5018A-07/08, H5020A-08/08, H5021A-09/08) and three new lots of Apotex product (Lot Nos.: HC3917, HC3918 and HC3939). It is believed that the higher variability in the spray pattern data observed with the Apotex product in the previously submitted data, causing the product to fail the PBE criterion, was due to the use of different lots of pump in the 3 batches of the Apotex product, and the likelihood that the three batches of RLD product utilized the same lot of pump (due to the fact that all three batches had the same expiry date). As a result, three batches of reference product, with different expiry dates, were chosen to try to ensure that different batches of pumps, as with the Apotex product, were likely to exist among the batches in order to provide a proper comparison of the two products. This was agreed to by the Agency during our telephone conference on December 22, 2005. The spray pattern Dmax and ovality ratio data were analyzed using the Population Bioequivalence Method employing $sigma_{TO}$ of 0.1 and epsilon of 0.01. The results indicate that the spray pattern of Apotex's product is equivalent to that of the reference product as the Population Bioequivalence criterion was met for both Dmax and ovality ratio. The summary of the statistical analysis is provided as Attachment No. 3. It is noteworthy that the variability of the data associated with the Apotex product is no longer higher than that of the reference product. This supports our proposition that the "failure" of our previously submitted data was not due to inequivalence of the two products but as a result of inequitable comparison of them. The use of the same testing method as with the previously submitted data also assures that the new data is not due to any change in the testing method.

The spray pattern data in SAS format is provided in the enclosed diskette and 20% representative spray pattern images are provided as Attachment No. 4.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:ml

Encl.

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May 15, 2006

MC

VIA ELECTRONIC TRANSMISSION
AND OVERNIGHT DELIVERY

Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

PRIVILEGED AND CONFIDENTIAL
ANDA COMMUNICATION, ANDA NO. 76-396

Re: Apotex Inc.'s ANDA No. 76-396 for
Calcitonin-Salmon Nasal Spray, 200IU/spray

Dear Mr. Buehler:

On behalf of our client Apotex Inc., we write to request that FDA: (1) grant final approval to Apotex's ANDA No. 76-396 as soon as the Agency determines that its current approval criteria have been satisfied; and (2) refrain from delaying approval while the Agency considers the scientifically baseless arguments contained in the September 2, 2005 citizen petition filed by Foley & Lardner LLP. Any other result will unlawfully deprive the public of access to an affordable generic product, cause Apotex to lose millions of dollars that it has invested in this product, and unfairly reward Foley's abuse of the citizen petition process.

On April 8, 2002, Apotex filed ANDA No. 76-396, which seeks approval to market a generic calcitonin-salmon nasal spray. FDA accepted that application for filing in July 2002. After accepting Apotex's application, the Agency has raised various issues regarding the application. Apotex has satisfactorily responded to each of FDA's inquiries.

By September 2005, it appeared, based upon Apotex's oral and written communications with the Agency, that all major outstanding issues regarding the application had

been addressed. Consequently, Apotex began to manufacture product in anticipation of receiving final approval in the near future. Apotex has, in fact, spent nearly [redacted] (b) (4) to manufacture [redacted] (b) (4) batches of finished product. As the Agency must know, this product has 2-year expiration dating. More importantly, product with less than 12-15 months of dating essentially is worthless because Apotex's customers will not purchase it. Thus, it is imperative that FDA approve Apotex's ANDA as soon as the Agency's current approval criteria have been satisfied, and that FDA not delay that approval while it fashions a response to the scientifically-meritless arguments made in the Foley petition.[1]

FDA often delays ANDA approval while it considers citizen petitions, no matter how baseless the petition. Brand companies know this and, especially over the last few years, have intentionally abused the citizen petition process by filing more and more generic-blocking petitions. The delay in resolving these petitions has lead to delayed ANDA approval and, thus, delayed generic market entry. Such delays are unacceptable. First, Congress enacted the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act in order "to get generic drugs into the hands of patients at reasonable prices – fast." *In re Barr Labs.*, 930 F.2d 72, 76 (D.C. Cir. 1991). Consequently, delaying ANDA approval until a citizen petition has been resolved runs contrary to congressional intent. Second, and more significantly, the Agency has no lawful basis for refusing to approve a pending ANDA that satisfies current Agency approval criteria. The simple fact is that nothing in the controlling statutory scheme permits FDA delay approval while it considers a citizen petition, and neither do FDA's own regulations. Indeed, the Agency's regulations make clear that the filing of a citizen petition does not stay any pending FDA action, particularly in the absence of a petition for stay of agency under 21 C.F.R. § 10.35.

FDA must approve Apotex's ANDA No. 76-396 as soon as the Agency determines that its current approval criteria have been met. The Agency cannot lawfully withhold final approval while it considers the anti-competitive and baseless petition filed by Foley in September 2005. Any other result would not only harm the public, but severely harm Apotex.

---

[1] Apotex has responded to FDA's December 2005 letter regarding spray pattern issues. With that response, FDA should be prepared to issue a final approval letter.

If you have any questions, or require any additional information, please do not hesitate to contact us.

Very truly yours,
RAKOCZY MOLINO MAZZOCHI SIWIK LLP

William A. Rakoczy

Christine J. Siwik

cc: Elizabeth Dickinson (via electronic transmission)
Robert West (via electronic transmission)

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

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July 14, 2006

MC

VIA ELECTRONIC TRANSMISSION
AND OVERNIGHT DELIVERY

Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

PRIVILEGED AND CONFIDENTIAL
ANDA COMMUNICATION, ANDA NO. 76-396

Re: Apotex Inc.'s ANDA No. 76-396 for
Calcitonin-Salmon Nasal Spray, 200IU/spray

Dear Mr. Buehler:

The follows up on our May 15, 2006 controlled correspondence, in which we requested, on behalf of our client Apotex Inc., that FDA: (1) grant final approval to Apotex's ANDA No. 76-396, which seeks approval to market a generic calcitonin-salmon (sCT) nasal spray, as soon as the Agency determines that its current approval criteria have been satisfied; and (2) refrain from delaying approval while the Agency considers the scientifically baseless arguments contained in the September 2, 2005 citizen petition filed by Foley & Lardner LLP.

Since our May 15 ANDA communication, Apotex has been informed that FDA has completed its review of Apotex's application and, further, that the Foley citizen petition is the only reason that the Agency has not finally approved Apotex's ANDA. As explained below and in our prior communication, FDA should not, and indeed cannot, delay Apotex's approval while it deals with Foley's meritless petition.

As we previously explained, in September 2005 it appeared, based upon Apotex's oral and written communications with the Agency, that all major outstanding issues regarding Apotex's application had been addressed. Consequently, Apotex began to manufacture product in anticipation of receiving final approval in the near future, spending nearly [redacted] (b) (4) to manufacture [redacted] (b) (4) batches of finished product. As the Agency must know, and as Apotex has explained, this product has 2-year expiration dating, and product with less than 12-15 months of

dating essentially is worthless because Apotex's customers will not purchase it. Thus, as we discussed, FDA must approve Apotex's ANDA as soon as the Agency's current approval criteria have been satisfied. Apotex believes that time has come.

On or about June 1, 2006, Apotex spoke with the project manager assigned to Apotex's application. During that call, the project manager stated that he did not see any outstanding issues with Apotex's ANDA. He stated that he was in the process of collecting all of the jackets from the various review teams, and that he would call if any issues arose upon review of those files. On or about June 13, 2006, Apotex received a message from the project manager. He confirmed that Labeling, Bio, and Chemistry are all acceptable. Significantly, he further confirmed that the only thing holding up FDA approval is the Foley citizen petition. Now that FDA has determined that Apotex's ANDA meets all current approval criteria, the Agency has no lawful basis for refusing to approve that application. As we have explained, nothing in the controlling statutory scheme permits FDA delay approval while it considers a citizen petition, and neither do FDA's own regulations. The Agency's regulations, in fact, make clear that the filing of a citizen petition does not stay any pending FDA action, particularly in the absence of a petition for stay of agency under 21 C.F.R. § 10.35. FDA, therefore, cannot continue delaying approval of Apotex's ANDA merely because Foley filed a petition. Rather, the Agency must approve that ANDA immediately. Any other result unfairly forces consumers to continue paying monopoly prices when an approvable, affordable generic alternative exists; costs Apotex millions of dollars; and unlawfully rewards Foley's anti-competitive abuse of the citizen petition process.

Further, FDA has had more than enough time to review the Foley petition and see it for what it is: a petition devoid of any scientific merit, filed for the sole purpose of delaying generic market entry. As an initial matter, the Agency, in denying a petition designed to delay approval of Unigene's recombinant salmon calcitonin application, has acknowledged that sCT has a simplistic structure and physicochemical structure characterization is a reasonable approach to identifying sameness of API: "Salmon calcitonin's relatively simple structure (it has only a limited secondary structure – a single disulfide bond) lends itself to physicochemical structural characterization." (FDA 8/12/05 Admin. Ruling in Docket 2004P-0015/CP1 at 8). Additionally, as FDA knows, the reference listed drug (RLD) here is a true solution intended for nasal inhalation. If a company formulates its generic drug product to be qualitatively (Q1) and quantitatively (Q2) the same as the RLD, as Apotex has done here, Foley offers the Agency no scientific justification for requiring *in vivo* bioequivalence testing. The Agency has outlined an extensive series of *in vitro* testing requirements for establishing the bioequivalence of inhalation solution in its *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, and for establishing chemistry sameness in its *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Drug Products*. Apotex has had conducted the required *in vitro* battery of tests and provided that data to FDA.

That data, as the Agency itself has determined, demonstrates that Apotex's proposed product is bioequivalent to the RLD.[1] And because Apotex's ANDA formulation is Q1 and Q2 the same as the RLD, Foley's claim that differing formulations and impurities/degradants could impact the bioavailability, safety, and efficacy of an ANDA product has no relevance here. Finally, Foley also requests safety comparability to Miacalcin®, including immunogenicity testing. But the Apotex product is synthetic, and Foley offers no scientific evidence that would compel the Agency to conclude that a synthetic active ingredient shown to be the same as that of the RLD, such as Apotex's here, nevertheless could show a possible difference in immunogenicity.[2] And, from a historical perspective, FDA already has approved at least two other peptide solution nasal sprays for systemic absorption (*e.g.*, desmopressin acetate) without the need for immunogenicity testing.

In the end, FDA has sufficient precedent and science to establish the approval criteria for a generic synthetic calcitonin salmon peptide solution for nasal inhalation. And, with respect to Apotex's ANDA, the Agency has applied that precedent and science when determining that Apotex's application is acceptable for approval. Now that FDA has made that determination, it should approve Apotex's ANDA No. 76-396. The Agency cannot lawfully withhold final approval while it considers Foley's anti-competitive and baseless petition – a petition that FDA could easily and quickly deny based upon its failure to present any scientific justification for the Agency to alter its established approval criteria for a product such as the one that Apotex seeks to market.

Apotex requests immediate final approval of its ANDA No. 76-396.

---

[1] As the Agency may have noticed in reviewing Apotex's application, the *in vitro* testing performed by Apotex on its sCT solution product is similar to that used to support the approval of another ANDA solution peptide product for systemic absorption, Desmopressin Acetate Nasal Inhalation. Apotex, and one other company, hold approvals for this product.

[2] FDA's administrative ruling on Unigene's product notes that Unigene performed a comparative immunogenicity study for its recombinant calcitonin product. (FDA 8/12/05 Admin. Ruling in Docket 2004P-0015/CP1 at 11). The Unigene product was manufactured using a recombinant production process, and did not involve a synthetic process that produced an identical active pharmaceutical ingredient.

If you have any questions, or require any additional information, please do not hesitate to contact us.

Very truly yours,
RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Christine J. Siwik

cc: Elizabeth Dickinson (via electronic transmission)
Robert West (via electronic transmission)

APOTEX CORP.

September 6, 2006

N/NC

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RE: ANDA # 76-396
Calcitonin-Salmon Nasal Spray, 200 IU/spray (Miacalcin Equivalent)
- Change in Point Of Contact Information

This letter is to notify FDA (Office of Generic Drugs) that we have hired a US Director of Regulatory affairs and thus, Mr. John Lay will be the primary point of contact, effective September 6, 2006 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

John G. Lay, B.Sc., RAC
Director, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston, FL 33326

Telephone: (954) 384-3987
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to me at the information above.

Sincerely,

Tammy McIntire

Tammy McIntire, M.S., R.Ph.
President

RECEIVED
SEP 11 2006
OGD / CDER

APOTEX CORP.

December 14, 2006

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

MC-

RE: Request for Meeting
(ANDA #76-396 Calcitonin-Salmon Nasal Spray (sCT), 200 IU/spray)

RECEIVED
DEC 15 2006
OGD/CDER

Dear Mr. Buehler,

Reference is made to the above-referenced product. Apotex hereby formally requests a face-to-face meeting with the Division to discuss the status of the above-referenced ANDA, the generic equivalent of Novartis' Miacalcin®, which is approved for the treatment of postmenopausal osteoporosis. This request is being conducted under 21CFR § 314.103.

The purpose of this meeting is to allow Apotex to better understand why CDER/OGD has delayed approval of Apotex's application because of purported concerns regarding the approval of such a product pursuant to an ANDA under Section 505(j) of the FFDCA. At this point, Apotex has not received information from FDA supporting these claims or purported concerns. As OGD has already conveyed, Apotex has satisfied all substantive requirements for approval of its ANDA.

Scientifically, sCT is a simple and well-characterized synthetic polypeptide that increases spinal bone mass. Apotex's ANDA for the product was filed on April 8, 2002. FDA accepted Apotex's ANDA for filing and review on July 17, 2002. In September 2005, OGD informed Apotex that all major approval issues had been addressed. Consequently, Apotex purchased (b) (4) of API and invested another (b) (4) to manufacture finished product for a commercial launch. Both the API and finished product have limited shelf life, which has already begun to expire. Apotex also risks losing its source of API. That same month, on September 2, 2005, a law firm, without identifying its client, filed a baseless citizen petition (CP) seeking to require generic sCT nasal products to conduct additional bioequivalence and safety testing, including immunogenicity testing.

On May 15, 2006, Apotex made a written submission to FDA requesting final approval, and stressing the imminent loss of inventory. On June 1 and 13, 2006, FDA confirmed that Apotex had satisfied all substantive requirements for approval, and that only the pending CP was delaying such approval. On July 14, 2006, Apotex made another written request to the FDA requesting final approval, and further addressing the frivolous arguments raised in the pending CP.

In August and September 2006, Agency personnel informed Apotex that approval was being delayed due to CDER concerns regarding the approval of such products via the ANDA route, despite OGD's support for the product.

2400 N. Commerce Parkway • Suite #400 • Weston, Florida 33326 • Phone: 1-800-706-5575 • Fax: 1-800-706-5576

Apotex's ANDA has been pending for over 4 years, even though Apotex admittedly satisfied all substantive requirements for approval of an ANDA as of September of 2005. Apotex now stands to lose its entire sCT investments (b) (4) together with its only source of API. Consumers are also suffering significant costs as they continue to pay monopoly prices for the brand product because of the Agency's refusal to approve Apotex's ANDA.

In sum, there is no legal or scientific reason for withholding approval of Apotex's ANDA. Accordingly, Apotex is respectfully requesting a meeting to discuss this matter with you so we can expedite approval of our sCT ANDA.

In order to resolve and expedite Apotex approval of ANDA #76-396, and also due to the numerous delays within FDA, Apotex respectfully request a meeting be held in the first week of January 2007. Additionally, the following list is provided of attendees we would like to speak to from FDA and also the project Apotex attendees.

FDA Requested Attendees:
Gary Buehler, Director, Office of Generic Drugs, CDER, FDA
Robert West, Deputy Director, Office of Generic Drugs, CDER, FDA
Dale Conner, Director, Division of Bioequivalence, Office of Generic Drugs, CDER, FDA

Apotex Attendees:
Bruce Clark, VP, Medical and Regulatory Affairs, Apotex Inc.
William A. Rakoczy, *Outside Counsel*
(b) (6) CSO, Biopharmaceuticals – Biostatistics, Apotex Inc.
Steven Giuli, Director, Government Affairs & Industry Relations, Apotex Corp.
John Lay, Director, Regulatory Affairs, Apotex Corp.
Gina Sirianni, Associate Director, Regulatory Affairs, Apotex Inc.

Thank you for your consideration of this request. I look forward to hearing from you regarding the possibility of scheduling a meeting to discuss this issue in person. Should you have any questions at all, please do not hesitate to call me directly at 954-384-3987.

Sincerely,

John G. Lay
Director, Regulatory Affairs
Apotex Corp.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIGINAL

February 20, 2007

N/AC

Mr. Benjamin Danso
Project Manager, Division of Chemistry I
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Danso:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Further to the telephone conference between FDA and Apotex Inc. on February 09, 2007, we are pleased to provide you with our response in quadruplet (Archival, Review, and Field copies, as well as a desk copy for yourself).

For ease of review, we have prepared our responses to your requests in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

Question 1:

(b) (4)

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.../cont'd

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

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Following this page, 4 pages withheld in full (b)(4)

Apotex's Calcitonin Salmon Nasal Spray does not pose any greater safety concern than does the RLD, Miacalcin®.

Please direct any communications regarding this amendment to John Lay at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3987 or fax: (954) 349-4233, or alternatively, please do not hesitate to contact myself at telephone: (416) 401-7889 or fax: (416) 401-3809.

Yours sincerely,

Per: Bernice Tao
Director, Regulatory Affairs US

BT:ml

Encl.

APOTEX CORP.

April 12, 2007

N/MC

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA # 76-396
Calcitonin-Salmon Nasal Spray, 200IU/spray
US Agent Change in Contact Information

We would like to notify FDA (Office of Generic Drugs) of a change in the contact information of our US Agent, effective April 1, 2007 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

Kiran Krishnan, MPharm, RAC
Project Leader, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston FL
33326

Telephone: (954) 384-3986
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3807.

Sincerely,

Bernice Tao
Director, Regulatory Affairs (US)

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Enclosure- Change in US Agent and Point Of Contact Information Letter

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIGINAL

July 23, 2007

ORIG AMENDMENT
N/AA

Mr. Benjamin Danso
Project Manager, Division of Chemistry I
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Danso:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

This Telephone Amendment is submitted in response to FDA's requests during the telephone conference between FDA and Apotex Inc. on March 02, 2007 regarding our Telephone Amendment submitted on February 20, 2007. Reference is also made to the following correspondence between Apotex and the Agency:

- Telephone conference on March 14, 2007
- E-mail correspondence from Bernice Tao to Benjamin Danso on March 20, 2007
- FDA fax dated March 30, 2007 in response to our e-mail dated March 20, 2007

For ease of review, we have prepared our responses in a Part A and Part B format. Part A addresses the comments provided in the telephone discussion of March 2, 2007 and Part B addresses the comments provided in the FDA fax of March 30, 2007.

This amendment is provided in quadruplet (Archival, Review, and Field copies, as well as a desk copy for yourself). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2. A copy of the FDA fax of March 30, 2007 is provided as Attachment 3.

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Following this page, 2 pages withheld in full (b)(4)-CCI/TS

.../cont'd

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(b) (4)

[redacted]

We trust that these additional studies satisfactorily address your concerns.

For any additional questions, please do not hesitate to contact me at tel: (416) 401-7889 or fax: (416) 401-3809. Alternatively, please contact Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (954) 384-3986 or fax: (954) 349-4233.

Yours sincerely,

Per: Bernice Tao
Director, Regulatory Affairs US

BT:ml

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

November 09, 2007

ORIG AMENDMENT

N/A

Dr. Benjamin Danso
Project Manager, Regulatory Support Branch
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Danso:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Apotex Inc. is hereby submitting a Telephone Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray in response to the phone conversation held between Bing Cai of FDA and Kiran Krishnan of Apotex Corp. on October 31, 2007.

For ease of review, we have prepared our response in a question-and-answer format. This amendment is provided in quadruplicate (Archival, Review, and Field copies, as well as a desk copy for yourself). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,
Apotex Inc.

Bernice Tao
Director, Regulatory Affairs US

BT:my

Encl.

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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
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November 28, 2007

Bing Cai
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AC

Dear Mr. Bing Cai:

Re: TELEPHONE AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Apotex Inc. is hereby submitting a Telephone Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray in response to your telephone request to myself on November 19, 2007.

For ease of review, we have prepared our response in a question-and-answer format. This amendment is provided in triplicate (Archival, Review, and Field copies). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,
Apotex Inc.

Bernice Tao
Director, Regulatory Affairs US

BT:gw

Encl.

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CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

NAI
2/13/08

January 16, 2008

Martin Shimer
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Shimer,

Re: PATENT AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396
US Patent Nos. 5,733,569 and 5,759,565

Apotex Inc. is hereby stating that the litigation with respect to US Patent Numbers is still in progress in the United States District Court for the Southern District of New York with reference to Civil Action No. 02-CV-8917.

Please note that Apotex's 30 month stay based on the notice sent to the patent holders ended on March 27, 2005. As such, we are requesting final approval of the ANDA application 76-396 for Calcitonin Salmon Nasay Spray.

If there are further concerns, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3807.

Sincerely,

Bernice Tao
Director – Regulatory Affairs (US)

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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
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April 30, 2008

ORIG AMENDMENT

N-000-AA

Bing Cai
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Bing Cai:

Re: GRATUITOUS AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDANo. 76-396

Apotex Inc. is hereby submitting a Gratuitous Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray in response to your telephone request to Kiran Krishnan on April 11, 2008 and further to a telephone discussion with myself on April 28, 2008. This amendment is provided in triplicate (Archival, Review, and Field copies). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

The drug substance and drug product specifications have been updated to comply with USP that becomes effective May 01, 2008. A summary of the changes has been provided in this Amendment. A commitment is provided that the drug substance and drug product will conform with the USP specifications.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,
Apotex Inc.

Bernice Tao
Director, Regulatory Affairs US

BT:gw

Encl.

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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

N/XP

ORIG AMEN

June 13, 2008

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Buehler:

Re: PATENT AMENDMENT
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396
US Patent Nos. 5,733,569 and 5,759,565

Apotex Inc. is hereby submitting a Patent Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray. An Application Form FDA 356h is enclosed as Attachment 1.

We wish to advise the FDA that litigation between Apotex Inc. and Novartis with respect to US Patent Nos. 5,733,569 and 5,759,565 has been dismissed by the United States District Court. A copy of the Stipulation of Dismissal has been included in Attachment 2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,
Apotex Inc.

for: Bernice Tao
Director, Regulatory Affairs US

BT:ks

Encl.

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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

July 18, 2008

Bing Cai
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N-AC

Dear Mr. Bing Cai:

Re: TELEPHONE AMENDMENT – USP Residual Solvents
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Apotex Inc. is hereby submitting a Telephone Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray in response to your telephone conversation today with myself. This amendment is submitted to provide information to meet the requirements of the USP General Chapter <467> *Residual Solvents* which became effective July 01, 2008. This amendment is provided in triplicate (Archival, Review, and Field copies). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

A detailed justification of potential residual solvents in Calcitonin-Salmon Nasal Spray manufactured by Apotex Inc. is provided in Attachment 3. Our study indicates that the drug product is within safety recommendations of the USP General Chapter <467> *Residual Solvents* and meets the requirements outlined in ICH Guideline Q3C(R3) *Impurities: Guideline for Residual Solvents.*

In addition, the current specification for Calcitonin Salmon USP/EP drug substance has been provided in Attachment 4 for reference. Please note that there have been no changes to the specification provided in our Gratuitous Amendment on April 30, 2008 other than the assignment of an issue number to the specification.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,

K. Stewart

for: Bernice Tao
Director, Regulatory Affairs US

BT:ks

Encl.

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JUL 21 2008
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APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

July 22, 2008

AA

Bing Cai
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Bing Cai:

Re: TELEPHONE AMENDMENT – USP Residual Solvents
Calcitonin-Salmon Nasal Spray, 200 IU/Spray; ANDA No. 76-396

Apotex Inc. is hereby submitting a Telephone Amendment to ANDA number 76-396 for Calcitonin-Salmon Nasal Spray, 200 IU/Spray in response to your telephone requests to myself on July 18, 2008 and July 21, 2008 to provide additional information to demonstrate compliance with the requirements of USP General Chapter <467> *Residual Solvents*.

For ease of review, we have prepared our response in a question-and-answer format. This amendment is provided in triplicate (Archival, Review, and Field copies). An Application Form FDA 356h is enclosed as Attachment 1 and a Field Copy Certification can be found as Attachment 2.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US

BT:ks

Encl.

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312.222.6321 Direct Fax
wrakoczy@rmmslegal.com

August 15, 2008

PRIVILEGED AND CONFIDENTIAL
ANDA COMMUNICATION, ANDA NO. 76-396

VIA E-MAIL
AND OVERNIGHT DELIVERY

MC

Gerald F. Masoudi
Chief Counsel, Office of Chief Counsel
Food and Drug Administration
5600 Fishers Lane, Room 605
Rockville, MD 20857

Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: Apotex Inc.'s ANDA No. 76-396 for Calcitonin-Salmon Nasal Spray, 200IU/spray

Dear Messrs. Masoudi and Buehler:

On behalf of Apotex Inc., we write to request immediate action on Apotex's ANDA No. 76-396 for calcitonin-salmon (sCT) nasal spray. This is Apotex's third such request. Our correspondence dated May 15, 2006, and July 14, 2006 remain unanswered. This is true even though Apotex has repeatedly been informed that agency review of its application is complete, and that no further information or data is required. Apotex is thus entitled to immediate final approval. We therefore request that FDA take immediate action on Apotex's ANDA, and no later than August 29, 2008. If the Agency does not take action on Apotex's ANDA by that time, Apotex will take appropriate legal action to enforce its rights.

As you know, Apotex's sCT ANDA has been pending before the Agency since July 2002, over some six years. To our knowledge, the only outstanding issue holding up Apotex's approval is a frivolous and anticompetitive citizen petition filed three years ago, in 2005, by Foley & Lardner LLP raising unfounded concerns over the approval criteria for generic calcitonin-salmon products solely to delay FDA approval of, and market entry by, generic applicants. Following the submission of this petition, FDA requested additional data from Apotex, which Apotex provided to the Agency by July 2007. Apotex therefore has gone above and beyond all substantive requirements for ANDA approval. In fact, for months now, FDA has repeatedly informed Apotex that the first generic review of its application is complete. Nevertheless, despite Apotex's repeated requests for approval and Agency action, FDA still has

not taken final action on Apotex's application due to the Agency's protracted consideration of Foley's meritless petition. Under the governing statutory and regulatory framework, however, this petition cannot lawfully delay final FDA approval. As such, Apotex is entitled to final approval *now*, not several weeks, months, or years from now.

For over a decade, courts have recognized that FDA need not rule on a pending citizen petition before approving an ANDA. *See Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 162 (D.D.C. 2006) (noting that Biovail "fails to offer any legal authority for the proposition that the defendant must rule on citizen petitions prior to approving an ANDA"); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 219 (D.D.C. 1996) ("Bristol has not pointed to and the court has found nothing in the FD&C Act that would require the FDA to first respond to a Petition before approving an ANDA.").

Indeed, in the *Biovail* case, FDA itself expressly conceded that "[n]one of the statutory or regulatory requirements mandate that FDA respond to a competitor's citizen petition before approving a product." (FDA Opp'n Br. at 8, Civ. A. No. 06-1487 (D.D.C.), attached hereto at Ex. A.) There, Biovail sought to enjoin FDA from issuing final approval to any generic Wellbutrin XL ANDA until after the Agency had acted on Biovail's citizen petition. Biovail argued that, if FDA were to approve any ANDA prior to ruling on the company's citizen petition, such action would deprive Biovail of its property interest in Wellbutrin XL. FDA opposed Biovail's motion and asserted that Biovail's "claim that FDA is somehow required to respond to its citizen petition before approving any ANDAs for generic Wellbutrin XL is groundless." (*Id.* at 1.) The Agency noted that "FDA only approves drug[] products if and when the statutory and regulatory requirements for safety and effectiveness have been satisfied. There is nothing in those requirements requiring a response to a citizen petition prior to approval." (*Id.* at 2.) FDA further clarified that, "under the statute, the agency *must* approve an application unless certain findings set out in the FDCA are identified[.]" (*Id.* at 8) (emphasis added).

FDA must adhere to its governing statute and regulations here. According to the Agency, Apotex has met the approval criteria for its sCT ANDA, meaning that "the statutory and regulatory requirements for safety and effectiveness have been satisfied." (*See id.* at 2.) Thus, "under the statute, the Agency must approve [Apotex's] application." (*See id.* at 8); *see also* 21 U.S.C. § 355(j)(4). Moreover, as FDA acknowledges, there is nothing in the controlling statutory scheme or FDA regulations that permit the Agency to delay Apotex's approval while it considers a citizen petition. Quite the contrary, FDA regulations make clear that the filing of a citizen petition does not stay any pending FDA action, particularly in the absence of a petition for stay. In addition, as you know, Congress recently sought to correct the improper or anticompetitive use of the citizen petition process to delay approval of important generic medicines through the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). The new statutory provisions, among other things, prohibit the Agency from delaying the approval of a pending application (such as Apotex's) due to the filing of a citizen petition, unless

the Agency determines that such delay is necessary to protect the public health. *See* 21 U.S.C. § 355(q)(1)(A). To our knowledge, the Agency has made no such determination here. Indeed, given the lack of merit to the Foley petition, no such determination could legitimately be made here. As such, FDA is statutorily obligated to approve Apotex's application without delay, and notwithstanding the existence of the Foley petition.

Congress enacted the new statutory provisions governing citizen petitions precisely to prevent the *exact* sort of delays Apotex has experienced—and is still experiencing—here. The legislative history of FDAAA reveals that the purpose behind these provisions was to "stop frivolous petitions from delaying generic entry . . . . [by] requiring the generic approval process to move forward while a petition is considered, unless the petition has raised legitimate public health concerns about the drug." (153 CONG. REC. S5454 (May 2, 2007) (statement of Sen. Stabenow), attached hereto at Ex. B; *see also* 153 CONG. REC. S5682 (May 8, 2007) (statement of Sen. Brown) (noting that the amendment "will stop drug companies from intentionally jamming up the [FDA] approval process for generic drugs, exploiting the citizen petition process to block price competition in the marketplace"), attached hereto at Ex. C.) In other words, Congress intended to "mak[e] certain that generic drug approvals are not delayed unnecessarily." (153 CONG. REC. S11840 (Sept. 20, 2007) (statement of Sen. Hatch), attached hereto at Ex. D.) Congress recognized that "FDA has a policy of not granting any new generic manufacturer's drug application until after it has considered and evaluated any citizen petitions regarding that drug." (153 CONG REC. S5490-91 (May 2, 2007) (statement of Sen. Kohl), attached hereto at Ex. E.) Congress further acknowledged that, "[t]he process of resolving a citizen petition, even if ultimately found to be groundless, can delay the approval by months or years" and that petitions are regularly filed "solely for the purpose of delaying the introduction of the generic competitor for the maximum amount of time possible." (Ex. E, 153 CONG. REC. S5491.) Congress thus proposed the citizen petition amendments to "fight back against the unjustifiable and costly delays caused by frivolous petitions submitted for the express purpose of blocking price competition in the marketplace" and "put a stop to a tactic which is as costly as it is unethical." (153 CONG. REC. S5474 (May 2, 2007) (statement of Sen. Brown), attached hereto at Ex. F.)

Foley's citizen petition is precisely the sort of "frivolous petition" Congress sought to deter. As we discussed in our correspondence dated July 14, 2006, Foley's petition has *not* "raised legitimate public health concerns about the drug;" is devoid of any scientific merit; and was filed for the sole purpose of delaying generic market entry. (*See* Ex. B, 153 CONG. REC. S5454.) Foley offers the Agency no scientific justification for requiring *in vivo* bioequivalence testing, and similarly offers no scientific evidence that would compel the Agency to conclude that a synthetic active ingredient shown to be the same as that of the RLD, such as Apotex's here, nevertheless could show a possible difference in immunogenicity. Indeed, the Agency already has approved generic drug products, such as desmopressin, that are extremely similar in nature to Apotex's proposed generic sCT product.

To Apotex's knowledge, but for Foley's citizen petition, Apotex's sCT ANDA would now be approved and Apotex would be on the market. Apotex's ANDA has been pending before the Agency for *over six years*. *Nearly three years ago*, in September 2005, all major outstanding issues regarding Apotex's ANDA appeared to have been addressed. *Over two years ago*, in June 2006, FDA informed Apotex that the Labeling, Bio, and Chemistry reviews were complete and acceptable and that the only thing holding up Apotex's ANDA was the Foley petition. *Last year*, by July 2007, Apotex provided a complete response to FDA's request for additional data. And, *for several months*, the Agency has confirmed (again and again) that the first generic review of Apotex's application is complete. The only outstanding issue related to Apotex's application is the petition filed by Foley *three years ago*.

The Agency's refusal to abide by Congress's mandate that FDA continue to review and act on generic drug applications notwithstanding any pending petitions is a flagrant violation of the statute. Congress specifically meant for the Agency to correct, not contribute to, the abuse of the generic drug approval process. The citizen petition provisions of FDAAA unquestionably were meant to benefit "businesses, consumers, and taxpayers—by allowing needed competition to bring down prices in the pharmaceutical market." (Ex. B, 153 CONG. REC. S5454.) As Senator Kennedy noted, "[t]he citizen petition provision is designed to address attempts to derail generic drug approvals. Those attempts, when successful, hurt consumers and the public health." (Ex. D, 153 CONG. REC. S11841.) That certainly is the case here. Apotex's application stands ready for final approval. Yet, FDA's disregard for its statutory obligations is unjustly costing consumers untold millions of dollars in drug savings that are going unrecognized due to its failure to approve Apotex's application.

The bottom line is that Apotex is entitled to action on its ANDA now. If we do not hear from the Agency by August 29, 2008, Apotex reserves all rights to pursue any and all appropriate legal remedies against the Agency. While Apotex trusts and hopes that this matter can be resolved without resort to legal action, the delays have gone on far too long for Apotex to wait any longer. Apotex already has lost millions of dollars in expired inventory, and even more importantly, the public is being denied a lower-priced generic version of this important medicine. We look forward to the Agency's prompt response.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

William A. Rakoczy

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 13, 2008

FROM: Andre Raw, Ph.D., Review Chemist, Office of Generic Drugs
Sau L. Lee, Ph.D., Chemical Engineer, Office of Generic Drugs

THROUGH: Gary Buehler, Director, Office of Generic Drugs

SUBJECT: N-1 Deletion Peptides are Impurities of Calcitinon

TO: ANDA 76-979 Nastech Pharmaceutical Company Inc.
ANDA 76-396 Apotex Inc.

N-1 deletion peptides are peptides missing one of the amino acids of the peptide's primary amino acid sequence. Calcitonin is a peptide composed of 32 amino acids, and this sequence of amino acids constitutes part of the standard for demonstrating sameness of the active ingredient. As N-1 deletion peptides of calcitonin are missing an amino acid present within calcitonin's amino acid sequence, they cannot be considered as part of the active ingredient; rather they should be considered as impurities of calcitonin. These assertions are further substantiated by several examples of NDAs for various peptide products approved by the Agency, which treat N-1 deletion peptides as impurities of the active ingredient. These examples are summarized below:

According to the EP monograph for salmon calcitonin,[1] the peptide related substances including N-1 deletion peptides are treated as impurities of calcitonin.[2] Additionally, as indicated in the CMC review of NDA 18-202, Supplement 021, the release specifications for the drug substance (calcitonin) used in the manufacture Miacalcin (calcitonin) for Injection control for impurities, including the N-1 deletion peptides based upon the EP monograph for calcitonin.

In addition to salmon calcitonin, N-1 deletion peptides are also treated as impurities of the active ingredient in other peptide products such as exenatide (NDA 21-773) and efuvirtide (NDA-21481). Exenatide and efuvirtide are 36 and 39 amino acid synthetic peptides, respectively. Controls on N-1 deletion impurities in these two NDA products are described in CMC reviews for both exenatide[3] injection and efuvirtide[4] injection.

In conclusion, N-1 deletion peptides are by-products of the manufacture of salmon calcitonin and are impurities of the salmon calcitonin active ingredient.

[1] European Pharmacopoeia 6.0, Calcitonin (Salmon) at 11372-1375 (2008).
[2] For example, the EP monograph lists for Impurity C as an impurity of calcitonin. Impurity C (des-22-tyrosine-calcitonin) is a N-1 deletion peptide related impurity that is missing tyrosine-22 (amino acid) from the sequence.
[3] For example in the NDA review for exenatide injection. (b) (4)
[4] For example in the NDA review for enfuvirtide injection, the FDA recommended that (b) (4)

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

/s/

Patricia L. Downs
11/17/2008 11:02:18 AM
SECRETARY

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-396 Applicant Apotex Inc
Drug Calcitonin Salmon Nasal Spray Strength(s) 200 IU/spray

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer**
Chief, Reg. Support Branch
Date 17 Jan 08 Date _____
Initials MHS Initials _____

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☒ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: ANDA submitted on 4/11/2002 based upon NDA 20313 with PIII certs to the '569 and '565 patents. RTR letter issued on 6/11/2002. ANDA ack for filing on 7/17/2002 (LO dated 9/16/2002). On 10/3/2002 the firm submitted PIV certs to both the '569 and '565 patents. CA 02 CV 8917 filed in the S District of NY on 11/8/2002 for infringement of the '569 and '565 patents. On 4/2/2003 the firm submitted RRs from Novartis Pharmaceuticals signed and dated 9/27/2002. As suit was filed within 45 days the 30 month stay of approval expires on 2/27/05. As of 1/16/2008 Apotex states that litigation remains ongoing. This application is eligible for 180 day exclusivity as the first applicant to provide PIV certs to both listed patents (pre-MMA submission)

ANDA is eligible for Full Approval with 180 day exclusivity.
I note that CP 2005P-0360 remains pending with the Agency and will need to be answered prior to OGDs' issuance of an approval action on this ANDA.

2. Project Manager, Ben Danso Team5
Review Support Branch
Date 1-15-08 Date REV ON 7-22-08
Initials BD Initials BD

Original Rec'd date 4-8-2002
Date Acceptable for Filing 7-17-2002
Patent Certification (type) P 4
Date Patent/Exclus.expires 3-31-2015
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12-29-07
Date of Office Bio Review 5-15-06
Date of Labeling Approv. Sum 3-9-06
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Acceptable Bio review tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer:
Date _____
Name/Initials _____
Comments:

Labeling Team Leader:
Date Wed 1/16/2008 10:08 AM
REV ON 7/22/2008
Name/Initials JFG

concur

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, January 15, 2008 8:28 PM
To: Danso, Benjamin; Grace, John F
Subject: RE: ANDA 76-396 (APOTEX Calcitonin Salmon)

John,

The labeling ap summary signed off 3/9/06 remains acceptable.

In response to the note to the chemist, Bing Cai stated that the stability data supports the recommended storage statements.

Ruby

-----Original Message-----
From: Danso, Benjamin
Sent: Tuesday, January 15, 2008 3:11 PM
To: Wu, Ruby (Chi-Ann); Grace, John F
Subject: ANDA 76-396 (APOTEX Calcitonin Salmon)

Ruby/ John,

Your blessing is needed for the subject ANDA to move forward on the approval chain. Attached is a copy of the labeling review.

Thanks

<< File: 76396.FPL.ap.pdf >>

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 1/28/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP ltr saved to V drive. Note - this can not issue until CP is resolved.

5. Div. Dir./Deputy Dir. Date1/28/08
Chemistry Div. I II OR III InitialsPS
Comments:cmc ok; firm commits to resolve mv issues

6. Frank Holcombe **First Generics Only** Date2/15/08
Assoc. Dir. For Chemistry InitialsRR
Comments: (First generic drug review)
cmc ok; this anda is Q1/Q2 to RLD, and not covered by CP. For Frank,

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date11/17/08
Director, DLPS Initialswpr
Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☒ No ☐; Petition: Yes☒ No☐
Comments:applicant made PIV patent certs to the '569 and '565 patents; litigation ongoing, 30 month stay expired 2/27/2005; eligible for full approval with 180 day exclusivity (pre MMA); no W/H exclusivity; Labeling acceptable per AP Summary 3/9/06 w/ team leader JG endorsement 7/22/08; Bio acceptable 5/15/06; EER acceptable 12/29/07

Okay for full approval

OR

8. Robert L. West
Deputy Director, OGD
Date _____
Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler
Director, OGD
Date _____
Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Ben Danso
Date 1-30-08; REV ON 7-22-08
Initials bd
Review Support Branch

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
_____Time notified of approval by phone
_____Time approval letter faxed

FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Benjamin Danso
11/18/2008 12:29:54 PM