

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-800

APPROVAL LETTER

ANDA 74-800

JUL 26 2001

Alpharma, U.S. Pharmaceuticals Division
Attention: Martin Levy
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated December 1, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cromolyn Sodium Nasal Solution USP, 5.2 mg cromolyn sodium delivered/spray, (40 mg/mL), packaged in 13 mL (100 metered spray) and 26 mL (200 metered spray) bottles.

Reference is also made to your amendments dated February 27, April 4, April 10, April 23, May 8, June 15, July 6, and July 16, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray, to be bioequivalent to the listed drug (NasalCrom[®] Nasal Spray, 5.2 mg cromolyn sodium/spray, of Pharmacia and Upjohn Consumer Healthcare).

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

Post-marketing reporting requirements for this abbreviated application 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.

Sincerely yours,



Gary Buehler 7/26/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

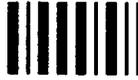
APPLICATION NUMBER:

74-800

APPROVED DRAFT LABELING

FORM 0075
VC1397

Nasal Allergy Symptom Controller
NASAL SOLUTION USP
CROMOLYN SODIUM
Nasal Spray



Nasal Spray
CROMOLYN SODIUM
NASAL SOLUTION USP
Nasal Allergy Symptom Controller

Nasal Allergy Symptom Prevention and Relief

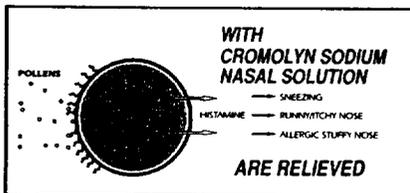
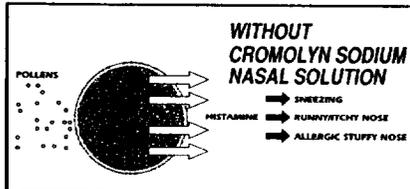
What Causes Nasal Allergy Symptoms?

Nasal allergies are caused by airborne pollens from trees, grasses or ragweed, and by molds, animals and dust. Exposure to these nasal allergy-causing substances may cause cells in your nose to release a substance called histamine. When histamine is released it causes nasal allergy symptoms: sneezing, runny/itchy nose, and allergic stuffy nose.

How Are Nasal Allergies Different From The Common Cold?

Some nasal allergy symptoms may seem like cold symptoms. But colds are caused by viral infections, and symptoms often include fever, body aches, discolored nasal discharge, or cough. It's rare for nasal allergies to produce these symptoms. If you have them, please call your doctor to see if Cromolyn Sodium Nasal Solution is right for you.

How May Cromolyn Sodium Nasal Solution Help?



Cromolyn Sodium Nasal Solution's formula works directly on the allergy sensitive cells in your nose to protect them from substances like pollens. Cromolyn Sodium Nasal Solution reduces the release of histamine, helping to decrease the allergic reaction before it starts. And with regular use, you get more protection.

To help prevent symptoms, start using Cromolyn Sodium Nasal Solution one week before contact with the cause of your nasal allergies.

▲ Cromolyn Sodium Nasal Solution works here



What Makes Cromolyn Sodium Nasal Solution Unique?

- 1. Prevention and relief.** Cromolyn Sodium Nasal Solution can relieve your nasal allergy symptoms and, if used as directed, can also prevent your symptoms.
- 2. Non-drowsy.** Many allergy medications contain antihistamines, which may cause drowsiness. Cromolyn Sodium Nasal Solution's formula works only in your nose and you don't get drowsy.
- 3. Builds protection.** Cromolyn Sodium Nasal Solution works by building protection against your nasal allergy symptoms. To maintain protection, continue to use Cromolyn Sodium Nasal Solution daily.
- 4. Can be used every day you need its protection.** Cromolyn Sodium Nasal Solution is a gentle nasal spray that works differently from decongestant sprays. Unlike those products, it continues to be safe and effective when used every day.
- 5. Can be used with other medications.** Cromolyn Sodium Nasal Solution can be used safely with other medications, including other allergy medications.

How To Use Cromolyn Sodium Nasal Solution Most Effectively

Cromolyn Sodium Nasal Solution works best at preventing your nasal allergy symptoms if you begin using it before your symptoms start.

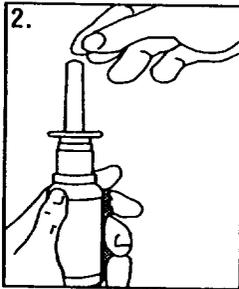
- For best results for prevention, start using Cromolyn Sodium Nasal Solution one week before contact with the cause of your allergies. For example, if you have hay fever, start using Cromolyn Sodium Nasal Solution one week before your peak nasal allergy season begins and use it every day throughout your season.
- To prevent symptoms from coming back, it is important to **continue** to use Cromolyn Sodium Nasal Solution every day while in contact with the cause of your nasal allergies, even when you are free of symptoms.
- **NOTE:** It may take several days of use to notice an effect. You may not get the full effect for 1-2 weeks. It is important to continue using Cromolyn Sodium Nasal Solution regularly.

- You should stop using Cromolyn Sodium Nasal Solution if you don't get relief within 2 weeks.
- If you need to use Cromolyn Sodium Nasal Solution for longer than 12 weeks, ask your doctor.
- Some people may get brief nasal stinging and/or sneezing right after the use of Cromolyn Sodium Nasal Solution.

Cromolyn Sodium Nasal Solution can be used every day. Doctors have prescribed it to millions of allergy sufferers to help control their nasal allergy symptoms.

How To Use The Pump Spray:

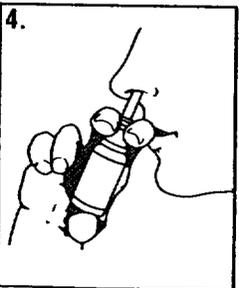
1. Blow your nose before using Cromolyn Sodium Nasal Solution.



2. Remove the clear plastic cap and white safety clip.



3. Hold pump with thumb at bottom and nozzle between fingers. **If this is the first time you are using the pump, spray 5 times into the air or until you get a fine mist. If you have not used the pump for 14 days, spray 2 times into the air before using again.**



4. Hold bottle as shown in picture. Insert nozzle into nostril. Spray upward while breathing in through the nose. This will release one dose of medication. Repeat in other nostril.

5. To keep clean, wipe the nozzle. Put clear plastic cap and white safety clip back on the bottle.
6. Do not share this bottle with anyone else as this may spread germs.

Some people may get brief nasal stinging and/or sneezing right after the use of Cromolyn Sodium Nasal Solution.

Nasal Allergy-Controlling Tips

- Many people are allergic to the dust mites that live in carpeting and bedding. Put mattresses and pillows in airtight covers and, if practical, get rid of all carpets. Use an air purifier with a HEPA (High Efficiency Particulate Air) filter to clean the air.

- People with nasal allergies to animals should limit their contact with these animals. It is the animal's dander (skin flakes) that causes allergies, not the hair length.

- People who are allergic to pollen and mold should use an air conditioner as much as possible. When you open the windows in your house, you let in pollen and mold spores.

Ask your doctor or health care professional for more tips on how to allergy-proof your home.

If you have any questions about **Cromolyn Sodium Nasal Solution**, ask your pharmacist.

Manufactured by Alphaforma USPD Inc., Baltimore, MD 21244

FORM NO. 0075

Rev. 2/98
VC1397

1.25 X 3.25 PANEL 3

HINGE

| | |
|--|--|
| <p>Active ingredient (per spray) Cromolyn sodium 5.2 mg</p> <p>Directions</p> <ul style="list-style-type: none"> • Parent or care provider must supervise the use of this product by young children • Adults and children 2 years and older: Spray once into each nostril (Repeat 3-4 times a day every 4-6 hours). If needed, may be used up to 6 times a day. Use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust). To prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact • Children under 2 years: Do not use unless directed by a doctor | <p>Purpose Nasal allergy symptom controller</p> |
|--|--|

1.25 X 3.25 PANEL 2

HINGE

| |
|---|
| <p>Other information • Store between 20°-25°C (68°-77°F)</p> <ul style="list-style-type: none"> • Keep away from light <p>Inactive ingredients benzalkonium chloride, edetate disodium, purified water</p> <p>Questions or comments? If you have any questions about Cromolyn Sodium Nasal Solution, ask your pharmacist</p> <p>See carton and package insert for full product information.</p> <p>Manufactured by Alpha USA Inc. Baltimore, MD 21244</p> |
|---|

1.25 X 3.25 PANEL 1 (CAN BLEED)

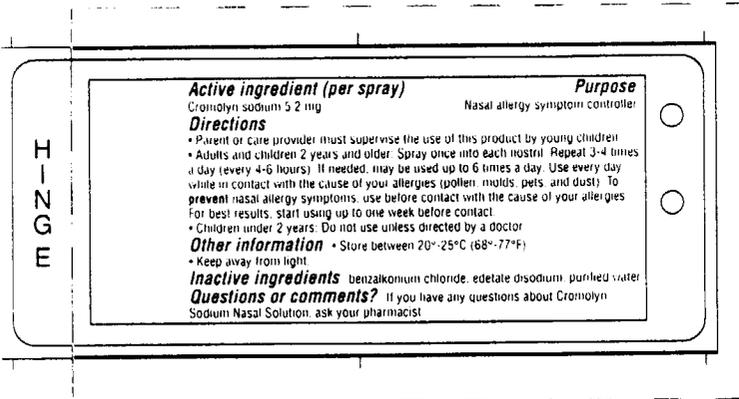
| | | | | |
|-------------------------------|--|---|---|----------------|
| 371 X 811 NON VARNISH AREA |  | <p>CROMOLYN SODIUM NASAL SOLUTION USP Nasal Allergy Symptom Controller</p> <p>Each spray delivers 5.2 mg cromolyn sodium (40 mg/mL cromolyn sodium)</p> <p>100 METERED SPRAYS 0.44 FL OZ (13 mL)</p> | <p>For intranasal use only See carton and package insert for full product information.</p> <p>Do not use if printed seals on carton end flaps were broken or missing.</p> <p>00750701 VC2073 Manufactured by Alpha USA Inc. Baltimore, MD 21244</p> | PEEL HERE → |
|-------------------------------|--|---|---|----------------|

1.25 X 3.25 PANEL DEADENER

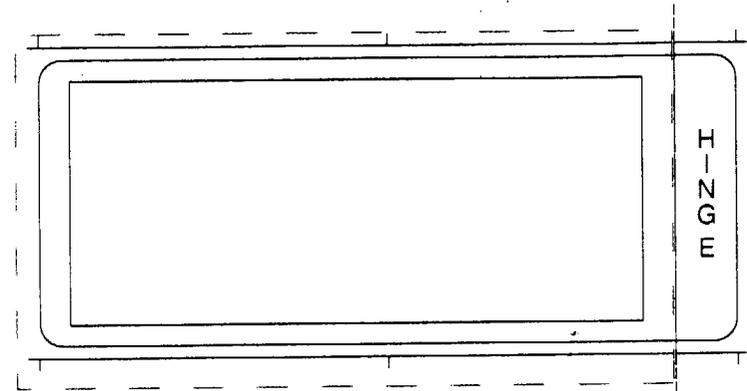
HINGE

PANEL DEADENER
DIE SIZE 1.25 X 3.25

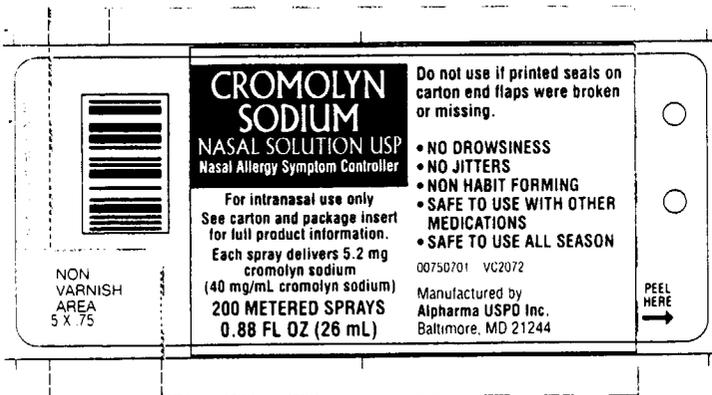
1.5 X 3.625 PANEL 3



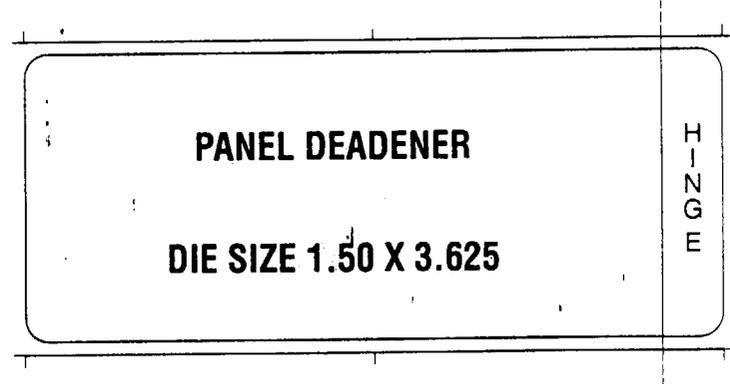
1.5 X 3.625 PANEL 2



1.5 X 3.625 PANEL 1-(CAN BLEED)



1.5 X 3.625 PANEL DEADENER





Both end flaps of this package are secured with a printed seal. Do not purchase if seal has been either removed or broken.

Cromolyn Sodium Nasal Solution USP
(Adults and Children 2 years and older)

Drug Facts

| Active ingredient (per spray) | Purpose |
|-------------------------------|----------------------------------|
| Cromolyn sodium 5.2 mg | Nasal allergy symptom controller |

Uses to prevent and relieve nasal symptoms of hay fever and other nasal allergies • runny/itchy nose • sneezing • allergic stuffy nose

Warnings

Do not use • if you are allergic to any of the ingredients

Ask a doctor before use if you have

• fever • discolored nasal discharge • sinus pain • wheezing

When using this product • it may take several days of use to notice an effect. Your best effect may not be seen for 1 to 2 weeks.

• brief stinging or sneezing may occur right after use
• do not use it to treat sinus infection, asthma, or cold symptoms
• do not share this bottle with anyone else as this may spread germs

Stop use and ask a doctor if

• shortness of breath, wheezing, or chest tightness occurs
• hives or swelling of the mouth or throat occurs
• your symptoms worsen • you have new symptoms
• your symptoms do not begin to improve within two weeks
• you need to use for more than 12 weeks

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

• see package insert on how to use pump
• parent or care provider must supervise the use of this product by young children
• adults and children 2 years and older
• spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day.
• use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust).
• to prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.
• if desired, you can use this product with other medicines, including other allergy medicines.
• children under 2 years: Do not use unless directed by a doctor. ▶

Drug Facts (continued)

Other information

• store between 20°-25°C (68°-77°F)
• keep away from light
• keep carton and package insert. They contain important instructions.

Inactive ingredients

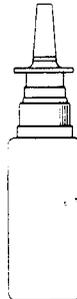
benzalkonium chloride edetate disodium, purified water

Questions?

If you have any questions about Cromolyn Sodium Nasal Solution, ask your pharmacist.

Before using any medication read all label directions. Keep carton and package insert. They contain important information.

Cromolyn Sodium Nasal Solution is convenient and easy to administer using the metered spray pump. See package insert for spray pump directions.



CROMOLYN SODIUM
NASAL SOLUTION USP
Nasal Allergy Symptom Controller



NDC 0472-0075-13

Compare to the active ingredient in **NasalCrom® Nasal Spray***

Nasal Spray

CROMOLYN SODIUM
NASAL SOLUTION USP
Nasal Allergy Symptom Controller

Prevents and Relieves Nasal Allergy Symptoms:

- runny/itchy nose
- sneezing
- allergic stuffy nose

Without Drowsiness
Full Prescription Strength

Safe For Ages 2 Years & Older

100 METERED SPRAYS
Each spray delivers 5.2 mg cromolyn sodium
0.44 FL OZ (13 mL)

What Makes Cromolyn Sodium Nasal Solution Unique?

Nasal Allergy Symptom Prevention

Cromolyn Sodium Nasal Solution can prevent nasal allergy symptoms when used before exposure to the cause of your nasal allergies, and will build protection against future symptoms as long as you continue to use Cromolyn Sodium Nasal Solution as directed.

Effective Relief

Cromolyn Sodium Nasal Solution provides original prescription-strength relief of nasal allergy symptoms, including congestion, sneezing and runny or itchy nose.

Works only in your nose

Cromolyn Sodium Nasal Solution is a nasal spray that works only in your nose—where nasal allergens attack. It helps to stop the cells in your nose from reacting to pollen, pet dander, and other allergens, so you don't experience nasal allergy symptoms.

Safe

- No drowsiness
- No jitters
- No "rebound" nasal congestion
- Safe to use with other medicines, including other allergy medicines
- Non habit forming
- Safe to use throughout your allergy season
- Good for year-round allergies
- Safe for children as young as two years old

* This product is not manufactured or distributed by Pharmacia & Upjohn Company, owner of the registered trademark NasalCrom®.

00750701C1 VC103942
Manufactured by **Alpharma USP Inc.**
Baltimore, MD 21244



Both end flaps of this package are secured with a printed seal. Do not purchase if seal has been either removed or broken.

Cromolyn Sodium Nasal Solution USP (Adults and children 2 years and older)

Drug Facts

Active ingredient (per spray) Cromolyn sodium 5.2 mg **Purpose** Nasal allergy symptom controller

Uses to prevent and relieve nasal symptoms of hay fever and other nasal allergies

- runny/itchy nose
- sneezing
- allergic stuffy nose

Warnings

Do not use if you are allergic to any of the ingredients

Ask a doctor before use if you have

- fever
- discolored nasal discharge
- sinus pain
- wheezing

When using this product

- It may take several days of use to notice an effect. Your best effect may not be seen for 1 to 2 weeks.
- Brief stinging or sneezing may occur right after use.
- Do not use it to treat sinus infection, asthma, or cold symptoms.
- Do not share this bottle with anyone else as this may spread germs.

Stop use and ask a doctor if

- Shortness of breath, wheezing, or chest tightness occurs
- Nives or swelling of the mouth or throat occurs
- Your symptoms worsen
- You have new symptoms
- Your symptoms do not begin to improve within two weeks
- You need to use for more than 12 weeks

If pregnant or breast-feeding, ask a health professional before use

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- See package insert on how to use pump
- Parent or care provider must supervise the use of this product by young children
- Adults and children 2 years and older
- Spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day.
- Use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust).
- To prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.
- If desired, you can use this product with other medicines, including other allergy medicines.
- Children under 2 years: Do not use unless directed by a doctor.

Drug Facts (continued)

Other information

- store between 20°-25°C (68°-77°F)
- keep away from light
- keep carton and package insert. They contain important instructions.

Inactive ingredients

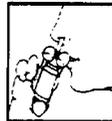
benzalkonium chloride, edetate disodium, purified water

Questions?

If you have any questions about Cromolyn Sodium Nasal Solution, ask your pharmacist.

Before using any medication read all label directions. Keep carton and package insert. They contain important information.

Cromolyn Sodium Nasal Solution is convenient and easy to administer using the metered spray pump. See package insert for spray pump directions.



CROMOLYN SODIUM NASAL SOLUTION USP Nasal Allergy Symptom Controller



NDC 0472-0075-36

Compare to the active ingredient in NasalCrom® Nasal Spray*

Nasal
Spray

CROMOLYN SODIUM NASAL SOLUTION USP Nasal Allergy Symptom Controller

Prevents and Relieves Nasal Allergy Symptoms:

- runny/itchy nose
- sneezing
- allergic stuffy nose

Without Drowsiness Full Prescription Strength

Safe For Ages 2 Years & Older

200 METERED SPRAYS

Each spray delivers 5.2 mg cromolyn sodium
0.88 FL OZ (26 mL)

What Makes Cromolyn Sodium Nasal Solution Unique?

Nasal Allergy Symptom Prevention

Cromolyn Sodium Nasal Solution can prevent nasal allergy symptoms when used before exposure to the cause of your nasal allergies, and will build protection against future symptoms as long as you continue to use Cromolyn Sodium Nasal Solution as directed.

Effective Relief

Cromolyn Sodium Nasal Solution provides original prescription-strength relief of nasal allergy symptoms, including congestion, sneezing and runny or itchy nose.

Works only in your nose

Cromolyn Sodium Nasal Solution is a nasal spray that works only in your nose—where nasal allergy attacks occur. It helps to stop the cells in your nose from reacting to pollen, pet dander, and other allergens you don't experience nasal allergy symptoms.

Safe

- No drowsiness
- No jitters
- No "rebound" nasal congestion
- Safe to use with other medicines, including other allergy medicines
- Non habit forming
- Safe to use throughout your allergy season
- Good for year-round allergies
- Safe for children as young as two years old

*This product is not the same as the product distributed by Alpharma & USPD, Inc. Company, owner of the registered trademark, NasalCrom®.

007507536

0100940

Manufactured by: Alpharma USPD Inc.
Baltimore, MD 21244

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-800

CHEMISTRY REVIEW(S)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-800 APPLICANT: AlpharmaDRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 40 mg/mL; 13 mL and 26 mL bottles

The deficiency presented below represents a MINOR deficiency.

1. Bioequivalence for this drug product has not been established. Please refer to the deficiencies from the Division of Bioequivalence dated February 5, 2001. If a new batch is manufactured in order to satisfy these deficiencies, a copy of the batch record including the in-process and release data for the batch must also be included.

Sincerely yours,

DS Gill

for

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

NOV 30 2000

38. Chemistry Comments to be Provided to the Applicant

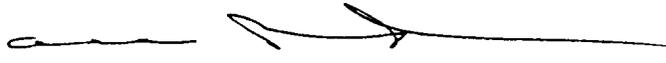
ANDA: 74-800 APPLICANT: Alpharma

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 40 mg/mL; 13 mL
and 26 mL bottles

The deficiency presented below represents a MINOR deficiency.

1. Bioequivalence for this drug product has not been established. Please refer to the attached deficiencies from the Division of Bioequivalence. If a new batch is manufactured in order to satisfy these deficiencies, a copy of the batch record, including the in-process and release data for the batch must also be included.

Sincerely yours,


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

OCT 14 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-800 APPLICANT: Alpharma

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 40 mg/mL; 13 mL and 26 mL bottles

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. The revised method for the Determination of the Number of Actuations, Weight per Actuation, and Unit Spray Content for Cromolyn Sodium Nasal Solution is not fully adequate. Since testing for these attributes is performed at the Beginning, Middle, and End for 3 units, and 6 additional units are tested at B, M, and E, at Tier 2, acceptance criteria should be based on an initial 9 evaluations (3 units x 3 determinations [B/M/E]), and a total of 27 evaluations (9 units x 3 determinations [B/M/E]) if Tier 2 testing is needed.

Please revise the method to reflect the actual number of determinations, or indicate that each determination includes a B/M/E evaluation, and if any of the evaluations fail, then the unit fails.

These comments pertain to release testing as well as stability testing.

2. Spray Pattern specifications (30 - 100 mm) are not adequate. The range is much too wide. Please propose appropriate specifications for Spray Pattern at release and on stability based on actual spray pattern results observed with the drug product.
3. Minimum Fill specifications are not appropriate. USP <755> specifications indicate that each of the 10 containers tested of aerosol drug products must meet the Minimum Fill. Please revise your Minimum Fill specifications accordingly.
4. Upon further reflection, we recommend that you establish a d_{90} specification for droplet size in addition to the d_{10} and d_{50} specifications in order to control excessively large droplets.

5. Particulate matter should also be evaluated on stability in addition to the release testing.
 6. Please submit a complete revised Finished Product Tests and Specifications sheet and Stability Specifications sheet updated to reflect all testing performed on release of the Finished Product and during the stability studies. Please update to include all of the revisions to the limits as well as references to the current test methods.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The referenced drug product will be manufactured in a newly constructed nasal spray manufacturing area in the firm's existing facility. Inspection of the facility as well as approval of the Process Validation Protocol, SOP's for the scale-up batches, and audit of the data fall within the purview of FDA field investigators, and will not be part of this review. An acceptable evaluation from the Office of Compliance is necessary prior to approval of the ANDA.

Sincerely yours,



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

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-800 APPLICANT: Alpharma

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 40 mg/mL; 13 mL and 26 mL bottles

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please update your Cromolyn Sodium drug substance tests and specifications to reflect modifications described in USP 23; Supplement #7. We also request that you submit representative spectra for the determination revised as per the Supplement.
2. Alpharma has indicated that samples of the bulk product will be evaluated for bioburden prior to the filling operation, however, bioburden limits have not been established for the bulk solution prior to filtration. Please establish appropriate criteria for evaluation of the microbial load during the manufacturing process but before the filtration/packaging process.
3. There is no evaluation of the performance of the filter system relative to its microbial retentivity. Even though the filter system for the drug product is not specifically utilized as a microbial retention filter, some evaluation of the filter integrity, combined with an evaluation of the bioburden of the pre-filtration solution, is necessary to evaluate the acceptability of the filtration process.
4. Please provide, in the batch record, information regarding the maximum time limit for completion of the filling operation.
5. Your packaging interchangeability protocol is not acceptable.

We continue to believe that interchangeability of components for a complex dosage form/delivery device which incorporates numerous elastomeric and plastic components using a multitude of compositional variations is not appropriate. We have the following recommendations:

- A. Interchangeability protocols for components manufactured from materials which have monographs for interchangeability in the USP (HDPE-to-HDPE, LDPE-to-LDPE, PET-to-PET and Glass-to-Glass) are acceptable.

- B. Fitments containing numerous individual components of varying composition (elastomeric gaskets, o-rings, rubber bulbs, teflon gaskets, etc.) and components incorporating other materials not covered by interchangeability monographs should be addressed individually. Due to the compositional differences, different impurities may be incorporated, which may result in an unknown effect on the drug product. In addition, changes in materials can have a dramatic effect on the performance of the delivery device and the subsequent delivery of the drug product.

Prior approval supplements will be required for such changes, since interchangeability cannot be adequately demonstrated. Additional studies may be necessary to characterize the new components which may not be part of the comparability protocols.

Please revise your interchangeability protocol accordingly.

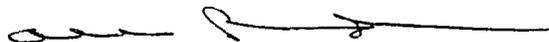
6. The **Number of Actuations** test method is not adequate to determine whether the unit can deliver the # of sprays indicated on the label (only 38 sprays are measured for the 100 metered spray bottle, and 88 for the 200 metered spray bottle. In addition, the method should evaluate whether the sprays are within QDS throughout the bottle's labeled contents. This is applicable for both release and stability testing.
7. The **Quantity Delivered per Spray** determination is performed by weighing before and after 8 actuations of the pump (after priming) and determining amount of cromolyn per volume of spray after conversion to volume and adjusting for cromolyn assay. We recommend the use of 2 sprays (one dose). We also recommend that the test be performed at various points in the bottle's use life (e.g. B/M/E of the bottle). Appropriate specifications should be established for the multiple testing on the individual bottles. In addition, an evaluation of QDS across multiple bottles (uniformity of dosage units test) should also be performed, and appropriate limits established. This is applicable for both release and stability testing.
8. We also recommend that a "shot weight" test be performed to assess the variability of the individual doses. This test may be performed in conjunction with the Quantity Delivered per Spray test, and 2 sprays (one dose) would be acceptable. This is applicable for both release and stability testing.

9. The **Minimum Fill** test specifications should be indicated. "Meets USP specifications" is not adequate.
10. *Pseudomonas Cepacia* should be tested for the microbial challenge (**APET**) test, and its absence included in the Microbial Limits test for release and stability.
11. Alpharma should delete the Edetate Disodium assay test from the stability protocol if it will not be performed as a stability test.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. We note that the drug product will be manufactured in a newly constructed nasal spray manufacturing area of the facility. Inspection of the facility as well as approval of the Process Validation Protocol, SOP's for the scale-up batches, and audit of the data fall within the purview of FDA field investigators, and will not be part of this review. An acceptable evaluation from the Office of Compliance is necessary prior to approval of the ANDA.
2. Your response must also address the labeling deficiencies.
3. Please submit additional long term stability data on the drug product beyond the 3 month stability test point to support the proposed expiration dating period of 24 months for both sizes, if available.

Sincerely yours,



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

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMISTRY REVIEW NO.: 7
2. ANDA #: 74-800
3. NAME AND ADDRESS OF APPLICANT:
Alpharma
Attention: Martin Levy, Director of Regulatory Affairs
Research and Development Center
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
4. LEGAL BASIS FOR SUBMISSION: Refer to C.R. #5.
5. SUPPLEMENT (s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME: Cromolyn Sodium
8. SUPPLEMENT (s) PROVIDE (s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
FIRM:
December 1, 1995 - Original ANDA Submission
February 27, 2001 - Bio Information
April 4, 2001 - ANDA Amendment - Proposal for Approval
April 10, 2001 - ANDA - Telephone Amendment; Bioequivalence Data.
April 11, 2001 - O-NC - Valois Spray Pump (3rd Party Submission)
April 23, 2001 - ANDA Telephone Amendment - Bioequivalence Data.
May 8, 2001 - ANDA Telephone Amendment - Bioequivalence Data.
*June 15, 2001 - ANDA MINOR Amendment (Response to 2/16/01 Action)
*July 6, 2001 - ANDA TELEPHONE Amendment (Response to 6/29/01
Telecon).
10. PHARMACOLOGICAL CATEGORY: Antiallergic (Allergic Rhinitis)
11. Rx or OTC: OTC status.
12. RELATED IND/NDA/DMF (s):
18-306 Fisons (Nasal cromolyn®)

ubstance

DMF #12525 - Valois VP-3 pump

13. DOSAGE FORM: Nasal Metered Spray 14. POTENCY: 4% (5.2 mg/actuation)

15. CHEMICAL NAME AND STRUCTURE: Refer to CR #5.

16. RECORDS AND REPORTS: N/A

17. COMMENTS

Alpharma has changed the actuator of the drug product to match the innovator delivery system. Firm has manufactured additional batches using the new actuators, and has provided batch records, CofA's and 2 month accelerated stability data on the drug product with the new actuator in 6/15/01 amendment.

Alpharma, in communications with OGD, was advised that an Amendment submitted to the ANDA changing the actuator would be acceptable for filing as a MINOR Amendment as per the Acting Director, OGD. However, the submission must be complete on its face. Alpharma USPD submitted the amendment without the 3 month accelerated stability study. Alpharma was contacted by Telephone on 6/29/01 and asked to submit 3rd month stability data on the 2 new batches, as well as data at B and E (rather than "average" data. Alpharma submitted the data in their 7/6/01 "Telephone Amendment".

18. CONCLUSIONS AND RECOMMENDATIONS: Approve

19. REVIEWER: Kenneth J. Furnkranz DATE COMPLETED: July 11, 2001

Page(s) 13

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Commercial/Confidential
Information and are not
releasable.

chem Rev. 7
7/11/01

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-800

Bioequivalence Review(s)

Cromolyn Sodium

Nasal Solution (26- & 13-mL Fill Sizes)

40 mg/mL (5.2 mg/ Actuation)

ANDA #74-800

Reviewer: Gur J.P. Singh

File name: 74800A.401

ALPHARMA

Cassel Drive

Baltimore, MD

Submission Dates:

February 27, April 4, 10 & 23,
and May 8, 2001

Review of Bioequivalency Amendments

Barre-National (ALPHARMA) initially submitted this application on December 1, 1995. The application contained a request for waiver of in vivo bioequivalence study requirements for its cromolyn sodium 5.2 mg/actuation nasal sprays (26- and 13-mL fill sizes), and in vitro data comparing performance of delivery devices of the test and reference (Nasal crom[®] Pharmacia and Upjohn, 5.2 mg/spray) products.

The Division of Bioequivalence (DBE) completed its review of this application on April 4, 1996. Based on that review, the firm was informed (letter date: April 16, 1996) that DBE had no further questions, and it was emphasized that the comments expressed in that letter were preliminary, which might be revised upon complete review of the application.

Though DBE completed its review previously, the "Office-Level" approval sheet was not prepared at that time. During preparation for the "Office-level" sign off, it was determined that the application was incomplete due to deficiencies in the Unit Dose (Uniformity of Dose), Priming and Repriming, and Droplet Size Distribution data. Therefore based on the November 21, 2000 amendment to the bioequivalency review, the firm was informed (letter date: November 29, 2000) of deficiencies in the in vitro data.

On December 11 and 22, 2000, the firm submitted its response to the deficiencies cited by DBE. Based the review of that response, the sponsor was informed (letter date: February 5, 2001) of the following:

1. *The prime retention (prime hold) data indicates that, after the 14-day storage period, the prime retention characteristics of the test product are not the same as that of the reference product. You are requested to repeat this test consistent with the reference product labeling. The primed units of the test and reference products should be stored for 14 days, and then reprimed by wasting 2 sprays. The amount of drug in the first spray after priming and the first spray after repriming should be determined for 10 units of each product.*
2. *The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product. The ratios of test/reference means are outside the limit stipulated in the draft Guidance for industry:*

Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action.

You may repeat the test using 10 units of each product. For determination of droplet size distribution by _____, please provide D10, D50, D90 and SPAN for individual units in an electronic spreadsheet. In addition please provide representative plots of percent transmission vs. time with D10, D50 and D90 vs. time on the same plot over the entire spray duration starting with the actuation trigger. These graphs should be labeled for the sampling time duration.

3. *The Division of Bioequivalence acknowledges lack of availability of certain information due to a proprietary agreement between the device supplier and the reference product manufacturer. However, for both the 26- and 13-mL products (test and reference), please provide measurements for the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter. In addition, you are requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.*

On February 27, 2001, the firm submitted its response to above deficiencies. The following comments are based on the review of those data:

Prime Retention/Loss of Prime: The reference listed drug's package insert states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before use. Therefore, the sponsor was requested to provide data supporting the sameness of prime retention characteristics of the test and reference products.

To determine prime retention characteristics the firm primed the test and reference products with five actuations. Spray #6 was collected and analyzed. Each unit was stored upright for 14 days. After that period, each unit was reprimed by wasting 2 sprays and the 3rd (9th from the beginning of use) spray was analyzed for the amount of drug per spray in 10 units of the test (Lot #PP0852F) and reference (Lot #49DYC) products. The results of prime retention testing are summarized in the following table:

| Spray # | Product | Mean | %CV | TEST/REF |
|-------------|---------|-------|-----|----------|
| 6 (Initial) | Test | 107.9 | 2.7 | 0.98 |
| | Ref | 110.1 | 3.1 | |
| 9 (14 days) | Test | 105.3 | 3.4 | 0.97 |
| | Ref | 108.5 | 3.4 | |

Based on the above data, the prime retention properties of the test product are similar to those of the reference product. Consistent with the repriming instructions given in the

RLD patient package insert, the test product also delivers the labeled amount of drug per actuation after a storage period of 14 days.

Droplet Size Distribution: The droplet size distribution of the test and reference products was studied using Malvern/Insitac at Beginning (immediately after priming), Middle (actuators 97-105) and End (actuators 152-160) sectors of product life. The test was performed at three distances (3, 6 and 12 cm) from the actuator orifice. The test and reference lot used in this testing were PP0852F and 65FDM (Exp. 8/02), respectively.

Annova automated actuator was used to actuate the test and reference products. The actuation parameters included the following:

| | |
|------------------|----------|
| Actuation force: | 4.5 kg, |
| Dose time: | 15 msec |
| Hold time: | 1 sec |
| Return time: | 20 msec. |

The following operating conditions were used for the Malvern/Insitac apparatus:

| | |
|-------------------------|-------------------|
| Test duration : | 300 msec |
| Data acquisition rate: | 1000 Hz |
| Acquisition duty cycle: | 0%, |
| Experimental trigger: | 95% transmission. |

The firm provided the raw D10, D50 D90 and SPAN data. It also provided the requested plots of Time vs. D10, D50, D90 and % transmission and computer outputs of the laser diffraction analyses.

The droplet size distribution data were found to be unacceptable. In a teleconference on March March 13, 2001, the firm was requested to repeat the test.

On March 23, March 2001, the sponsor indicated that it wished to replace actuator on the test product. The firm was informed that it should repeat three in vitro tests including Unit Spray Content, Droplet Size distribution and Spray pattern.

The sponsor submitted data regarding above tests on April 4 and 10, 2001. A brief survey of that submission indicated that supporting data for unit dose and spray pattern were still not submitted. On April 13, 2001 the firm was requested to submit the required data. The firm's response was submitted on April 23, 2001, which was still deficient. On May 7, 2001, the firm was requested to address the Agency questions on spray pattern testing included in the April 23 submission. The firm submitted its response on May 8, 2000. The following review is based on the information submitted April 4, 10, 23 and May 8, 2001.

Unit Spray Content

The Unit Spray Content determinations were based on analysis of single actuations of the primed units of test and reference products, at the beginning (actuations 6 & 7) and end (actuations 204 & 205). The units were actuated using AnnovaSystem's automated actuators operated at the following parameters:

Actuation force: 5 kg
 Dose time: 25 msec
 Return time: 20 msec
 Hold time: 1 sec
 Delay time: 1 sec

The following table provides a summary of the unit spray data:

| Sector | Product | Arith. Mean | %CV | Geomean | Test/Ref | | |
|--------|---------|-------------|------|---------|-------------|---------|---------|
| | | | | | Arith. Mean | Geomean | p-value |
| Beg | Test | 107.86 | 6.48 | 107.64 | 1.04 | 1.03 | 0.12 |
| | Ref | 104.18 | 2.69 | 104.14 | | | |
| End | Test | 111.98 | 3.74 | 111.91 | 1.05 | 1.05 | 0.01 |
| | Ref | 106.42 | 1.26 | 106.41 | | | |

Based on the above data, the unit spray content of the test product is within the acceptable range of 0.9-1.11 stipulated in the draft BA/BE guidance and used by the Division of Bioequivalence for evaluations of similar data on other solution nasal spray applications.

A review of the raw data indicated that the Unit Spray Content data also conformed to the following recommendations in the draft guidance regarding the 'first-tier' based on 10 units:

Not more than one unit should be outside of the label claim, and none should be outside the and

Mean values should not outside 85-115%.

Droplet Size Distribution

The droplet size distribution was studied based on testing conditions mentioned above. Based on % transmission the plume was divided into three portions (initial middle, and dissipating). The middle portion represents the fully formed plume where obscuration of the laser beam highest and stable relative to that of the other two portions. In other applications currently under review, for determination of equivalence, the DBE is using the D50 and Span data for the fully formed plume. The following tables provide a summary of the D50 and SPAN data for the fully formed plume:

| D50 | | | | | | | | |
|---------|----------|--------|-------------|------|---------|-------------|---------|---------|
| Product | Distance | Sector | Arith. Mean | % CV | Geomean | Test/Ref | | p-value |
| | | | | | | Arith. Mean | Geomean | |
| TEST | 3 Cm | Beg | 37.49 | 5.94 | 37.42 | 1.02 | 1.02 | 0.3446 |
| | | Mid | 35.82 | 6.98 | 35.74 | 1.00 | 1.00 | 0.8209 |
| | | End | 36.67 | 5.57 | 36.61 | 1.01 | 1.01 | 0.4370 |
| REF | 3 Cm | Beg | 36.90 | 6.41 | 36.83 | | | |
| | | Mid | 35.99 | 7.27 | 35.90 | | | |
| | | End | 36.22 | 6.27 | 36.15 | | | |
| TEST | 6 Cm | Beg | 38.27 | 2.02 | 38.26 | 1.02 | 1.02 | 0.0047 |
| | | Mid | 38.36 | 3.35 | 38.33 | 1.01 | 1.01 | 0.1430 |
| | | End | 38.92 | 3.82 | 38.89 | 1.03 | 1.03 | 0.0026 |
| REF | 6 Cm | Beg | 37.59 | 2.71 | 37.57 | | | |
| | | Mid | 37.90 | 3.19 | 37.88 | | | |
| | | End | 37.65 | 4.23 | 37.62 | | | |
| TEST | 12 Cm | Beg | 51.24 | 8.75 | 50.97 | 1.01 | 1.01 | 0.4694 |
| | | Mid | 51.67 | 4.78 | 51.61 | 1.04 | 1.04 | 0.0006 |
| | | End | 51.76 | 3.76 | 51.73 | 1.04 | 1.04 | 0.0004 |
| REF | 12 Cm | Beg | 50.59 | 3.72 | 50.56 | | | |
| | | Mid | 49.50 | 5.28 | 49.43 | | | |
| | | End | 49.77 | 4.22 | 49.73 | | | |

SPAN

| Product | Distance | Sector | Arith. Mean | % CV | Geomean | Test/Ref | | p-value |
|---------|----------|--------|-------------|-------|---------|-------------|---------|---------|
| | | | | | | Arith. Mean | Geomean | |
| TEST | 3 Cm | Beg | 1.72 | 7.01 | 1.72 | 1.00 | 1.00 | 0.8394 |
| | | Mid | 1.76 | 5.69 | 1.75 | 0.99 | 0.99 | 0.4445 |
| | | End | 1.76 | 5.36 | 1.75 | 0.98 | 0.98 | 0.2870 |
| REF | 3 Cm | Beg | 1.73 | 8.28 | 1.72 | | | |
| | | Mid | 1.78 | 8.39 | 1.78 | | | |
| | | End | 1.79 | 9.02 | 1.78 | | | |
| TEST | 6 Cm | Beg | 1.13 | 9.31 | 1.13 | 0.94 | 0.94 | 0.0257 |
| | | Mid | 1.15 | 8.86 | 1.15 | 0.98 | 0.98 | 0.4875 |
| | | End | 1.16 | 7.56 | 1.16 | 0.98 | 0.98 | 0.3279 |
| REF | 6 Cm | Beg | 1.20 | 10.08 | 1.19 | | | |
| | | Mid | 1.17 | 11.32 | 1.16 | | | |
| | | End | 1.19 | 11.39 | 1.18 | | | |
| TEST | 12 Cm | Beg | 1.10 | 5.79 | 1.09 | 1.06 | 1.06 | 0.0008 |
| | | Mid | 1.02 | 5.16 | 1.02 | 0.98 | 0.98 | 0.1401 |
| | | End | 1.02 | 5.57 | 1.02 | 0.99 | 0.99 | 0.6017 |
| REF | 12 Cm | Beg | 1.03 | 6.27 | 1.03 | | | |
| | | Mid | 1.05 | 6.61 | 1.04 | | | |
| | | End | 1.03 | 7.55 | 1.03 | | | |

Based on the above data:

The test/reference geometric mean ratios for the D50 data are within the acceptable the limit of stipulated in the draft Nasal BA/BE guidance. The test and reference products exhibited approximately the same variability (%CV) in D50.

The test/reference geometric mean ratios for the SPAN data are within the acceptable the limit stipulated in the draft Nasal BA/BE guidance. The test and reference products exhibited approximately same variability (%CV) in SPAN.

Droplet size distribution conducted by the firm is acceptable.

In the March 13, 2001 teleconference the firm was also requested to provide data regarding duration of the test and reference product's fully formed plume as well as the entire spray. These data were requested for information only, *not to be used in determination of equivalence of in vitro performance*. Reviewer's summary of the plume duration data is as follows:

| Distance | Sector | Product | Plume Duration (sec) | | TEST/REF | | |
|----------|-----------|---------|----------------------|--------------|----------------|--------------|------|
| | | | Stable Portion | Entire Spray | Stable Portion | Entire Spray | |
| 3 | Beginning | TEST | Mean | 0.095 | 0.200 | 0.92 | 1.09 |
| | | | %CV | 10.291 | 12.071 | | |
| | | | Geomean | 0.094 | 0.199 | 0.92 | 1.09 |
| | | REF | Mean | 0.103 | 0.183 | | |
| | | | %CV | 6.443 | 10.950 | | |
| | | | Geomean | 0.102 | 0.182 | | |
| 3 | Middle | TEST | Mean | 0.105 | 0.172 | 0.95 | 1.03 |
| | | | %CV | 5.523 | 3.721 | | |
| | | | Geomean | 0.105 | 0.172 | 0.95 | 1.03 |
| | | REF | Mean | 0.111 | 0.167 | | |
| | | | %CV | 6.461 | 5.595 | | |
| | | | Geomean | 0.111 | 0.167 | | |
| 3 | End | TEST | Mean | 0.123 | 0.174 | 1.10 | 1.02 |
| | | | %CV | 5.693 | 3.877 | | |
| | | | Geomean | 0.123 | 0.174 | 1.10 | 1.02 |
| | | REF | Mean | 0.112 | 0.171 | | |
| | | | %CV | 5.151 | 5.505 | | |
| | | | Geomean | 0.112 | 0.171 | | |
| 6 | Beginning | TEST | Mean | 0.097 | 0.194 | 0.92 | 1.01 |
| | | | %CV | 6.578 | 5.796 | | |
| | | | Geomean | 0.097 | 0.194 | 0.92 | 1.01 |
| | | REF | Mean | 0.106 | 0.192 | | |
| | | | %CV | 6.185 | 5.461 | | |
| | | | Geomean | 0.105 | 0.192 | | |
| 6 | Middle | TEST | Mean | 0.103 | 0.197 | 0.91 | 1.03 |
| | | | %CV | 5.387 | 5.933 | | |
| | | | Geomean | 0.103 | 0.196 | 0.91 | 1.03 |
| | | REF | Mean | 0.114 | 0.191 | | |
| | | | %CV | 8.347 | 5.110 | | |
| | | | Geomean | 0.113 | 0.191 | | |
| 6 | End | TEST | Mean | 0.107 | 0.200 | 1.00 | 1.05 |
| | | | %CV | 7.050 | 5.625 | | |
| | | | Geomean | 0.107 | 0.200 | 1.01 | 1.05 |
| | | REF | Mean | 0.107 | 0.191 | | |
| | | | %CV | 11.429 | 5.587 | | |
| | | | | | | | |

| | | Geomean | 0.106 | 0.191 | | | |
|----|-----------|---------|---------|--------|-------|------|------|
| 12 | Beginning | TEST | Mean | 0.128 | 0.290 | 1.21 | 1.51 |
| | | | %CV | 12.587 | 4.922 | | |
| | | | Geomean | 0.127 | 0.290 | 1.20 | 1.51 |
| | REF | Mean | 0.106 | 0.192 | | | |
| | | %CV | 6.185 | 5.461 | | | |
| | | Geomean | 0.105 | 0.192 | | | |
| 12 | Middle | TEST | Mean | 0.100 | 0.295 | 0.95 | 1.54 |
| | | | %CV | 3.074 | 2.564 | | |
| | | | Geomean | 0.100 | 0.295 | 0.95 | 1.54 |
| | REF | Mean | 0.106 | 0.192 | | | |
| | | %CV | 6.185 | 5.461 | | | |
| | | Geomean | 0.105 | 0.192 | | | |
| 12 | End | TEST | Mean | 0.108 | 0.288 | 1.02 | 1.50 |
| | | | %CV | 7.088 | 5.913 | | |
| | | | Geomean | 0.107 | 0.287 | 1.02 | 1.50 |
| | REF | Mean | 0.106 | 0.192 | | | |
| | | %CV | 6.185 | 5.461 | | | |
| | | Geomean | 0.105 | 0.192 | | | |

The above data are presented for information only, no comments are warranted.

Spray Pattern

The firm submitted spray pattern data for 10 units of the test and reference products. The units were actuated using Annova System's automated actuators operated at the following parameters:

Actuation force: 4.5 kg
Dose time: 30 msec
Return time: 20 msec
Hold time: 0.5 sec

The sprays were actuated on to chromatography paper at distances of 3, 5 and 7 cm from the orifice. The patterns of dried sprays were visualized using 2,3,5-triphenyltetrazolium chloride solution in methanol. The firm submitted color photocopies showing images of spray patterns with lines indicating Dmax and Dmin.

The patterns were manually quantitated in terms of longest diameter (Dmax), shortest diameter (Dmin) and Ovality ratio (Dmax/Dmin). The following table provides the reviewer's summary of the spray pattern data:

| Distance | Parameter | Product | Sector | Arith. Mean | % CV | Geomean | Test/Ref | | p |
|----------|-------------|---------|--------|-------------|-------|---------|-------------|---------|-------|
| | | | | | | | Arith. Mean | Geomean | |
| 3 | Dmax | TEST | Beg | 5.03 | 8.94 | 5.01 | 0.99 | 0.99 | 0.835 |
| | | | End | 4.55 | 8.17 | 4.54 | 1.01 | 1.01 | 0.778 |
| | | REF | Beg | 5.07 | 5.50 | 5.06 | | | |
| | | | End | 4.50 | 6.54 | 4.49 | | | |
| | Dmin | TEST | Beg | 4.18 | 12.24 | 4.15 | 0.95 | 0.95 | 0.369 |
| | | | End | 3.78 | 7.67 | 3.77 | 1.10 | 1.10 | 0.016 |
| | | REF | Beg | 4.38 | 9.67 | 4.36 | | | |
| | | | End | 3.44 | 4.59 | 3.44 | | | |
| | Oval. Ratio | TEST | Beg | 1.22 | 14.87 | 1.21 | 1.05 | 1.04 | 0.396 |
| | | | End | 1.21 | 5.80 | 1.20 | 0.92 | 0.92 | 0.049 |
| | | REF | Beg | 1.16 | 6.08 | 1.16 | | | |
| | | | End | 1.31 | 7.80 | 1.31 | | | |
| 5 | Dmax | TEST | Beg | 6.68 | 10.32 | 6.65 | 0.99 | 0.99 | 0.835 |
| | | | End | 6.42 | 9.45 | 6.39 | 0.99 | 0.99 | 0.811 |
| | | REF | Beg | 6.73 | 8.69 | 6.71 | | | |
| | | | End | 6.49 | 6.79 | 6.48 | | | |
| | Dmin | TEST | Beg | 5.71 | 9.06 | 5.69 | 1.01 | 1.01 | 0.828 |
| | | | End | 5.46 | 8.11 | 5.44 | 1.04 | 1.04 | 0.404 |
| | | REF | Beg | 5.68 | 10.62 | 5.65 | | | |
| | | | End | 5.27 | 12.90 | 5.23 | | | |
| | Oval. Ratio | TEST | Beg | 1.17 | 9.87 | 1.17 | 0.99 | 0.98 | 0.751 |
| | | | End | 1.18 | 7.02 | 1.17 | 0.95 | 0.95 | 0.196 |
| | | REF | Beg | 1.19 | 8.77 | 1.19 | | | |
| | | | End | 1.24 | 9.81 | 1.24 | | | |
| 7 | Dmax | TEST | Beg | 8.37 | 7.70 | 8.35 | 1.05 | 1.05 | 0.302 |
| | | | End | 7.95 | 5.97 | 7.94 | 1.00 | 1.00 | 1.000 |
| | | REF | Beg | 7.96 | 8.52 | 7.94 | | | |
| | | | End | 7.95 | 6.31 | 7.94 | | | |
| | Dmin | TEST | Beg | 6.73 | 9.98 | 6.70 | 1.08 | 1.08 | 0.089 |
| | | | End | 6.40 | 6.91 | 6.39 | 1.05 | 1.05 | 0.216 |
| | | REF | Beg | 6.24 | 8.55 | 6.22 | | | |
| | | | End | 6.12 | 10.47 | 6.09 | | | |
| | Oval. Ratio | TEST | Beg | 1.25 | 7.05 | 1.25 | 0.97 | 0.98 | 0.531 |
| | | | End | 1.25 | 7.92 | 1.24 | 0.95 | 0.95 | 0.292 |

| | | | | |
|-----|-----|------|-------|------|
| REF | Beg | 1.28 | 10.12 | 1.28 |
| | End | 1.31 | 12.87 | 1.30 |

In the above data test/ref ratios based on geometric means were within the range stipulated in the draft Nasal BA/BE guidance. The variability of the test and reference products was comparable. These data are indicative of comparable spray patterns of test and reference products.

Device Comparability

The ALPHARMA product uses the Valois pump (5) and actuator. The innovator product uses similar pump and actuator manufactured by Valois. Comparability of the delivery devices used in the test and reference product is also evident from comparable performance based on the in vitro testing.

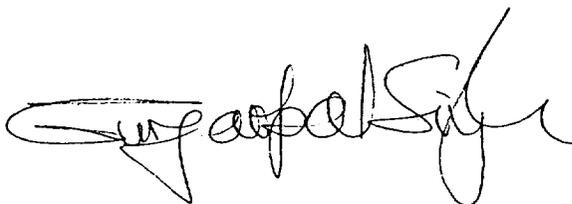
Overall Comments

1. The formulation of the test and reference products have been previously found to be qualitatively (Q₁) and quantitatively (Q₂) the same as that of the reference product (see the April 4, 1996 DBE review).
2. The Priming and Tail off data are acceptable. The Prime Retention (prime hold) data indicates that the prime retention characteristics of the test product after the 14-day storage period are the same.
3. Based on the Unit Spray Content data, Droplet Size Distribution data, and Spray pattern analyses reviewed herein, the in vitro performance of the test product is within the range stipulated in the draft guidance. The plume geometry data were found to be acceptable previously.
4. This application was initially submitted several years before the issuance of the June 99 draft nasal BA/BE guidance. Therefore, it is based on in vitro data from single lots of the test and reference products. The criteria used for evaluation of the test are similar to those used for other nasal spray applications (ANDA 74-830 and 75-702) submitted before issuance of the draft guidance. Comparability of in vitro performance of the test and reference products was established based on ratios of geometric means and consideration of relative variability of these drug products.

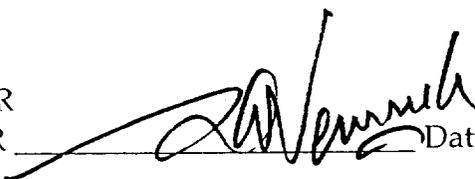
Recommendation

The formulations of the test product is Q1 and Q2 the same as that of the reference product. The in vitro testing conducted by Barre-National (ALPHARMA) comparing its cromolyn sodium nasal sprays (5.2 mg/spray, 26- and 13-mL fill sizes) and the reference product (Nasalcrom[®], Pharmacia and Upjohn, 5.2 mg/spray) has been found to be acceptable to the Division of Bioequivalence. In terms of dose delivered per actuation, the size shape and droplet size distribution of the spray, the test product's performance is similar to that of the reference product. Therefore the Division of Bioequivalence deems the test product to be equivalent to the reference product in dose delivery and performance of the delivery device.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence



RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR



Date 5/10/2001

Concur:  Date 5/31/2001

 Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-800

APPLICANT: ALPHARMA

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL
(26 and 13-mL fill sizes)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-800

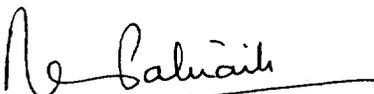
APPLICANT: ALPHARMA

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL
(26 and 13-mL fill sizes)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,


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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-800

APPLICANT: ALPHARMA

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL

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 prime retention (prime hold) data indicates that, after the 14-day storage period, the prime retention characteristics of the test product are not the same as that of the reference product. You are requested to repeat this test consistent with the reference product labeling. The primed units of the test and reference products should be stored for 14 days, and then reprimed by wasting 2 sprays. The amount of drug in the first spray after priming and the first spray after repriming should be determined for 10 units of each product.
2. The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product. The ratios of test/reference means are outside the 90-111% limit stipulated in the draft *Guidance for industry: Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action*.

You may repeat the test using 10 units of each product. For determination of droplet size distribution by laser diffraction please provide D10, D50, D90 and SPAN for individual units in an electronic spreadsheet. In addition please provide representative plots of percent transmission vs. time with D10, D50 and D90 vs. time on the same plot over the entire spray duration starting with the actuation trigger. These graphs should be labeled for the sampling time duration.

3. The Division of Bioequivalence acknowledges lack of availability of certain information due to a proprietary agreement between the device supplier and the reference product manufacturer. However, for both the 26- and 13-mL products (test and reference), please provide measurements for the metering chamber volume, dip tube internal diameter,

actuator tip length and orifice diameter. In addition, you are requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.

Sincerely yours,

A handwritten signature in cursive script that reads "Dale P. Conner".

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

Cromolyn Sodium

Nasal Solution (26- & 13-mL Fill Sizes)

40 mg/mL (5.2 mg/ Actuation)

ANDA #74-800

Reviewer: Gur J.P. Singh

File name: 74800A.D00

ALPHARMA

Cassel Drive

Baltimore, MD

Submission Dates:

11 and 21 December 2000

Review of Bioequivalency Amendments

Barre-National (ALPHARMA) submitted this application on 1 December 1995. The application contained a request for waiver of in vivo bioequivalence study requirements for its cromolyn sodium 5.2 mg/actuation nasal sprays (26- and 13-mL fill sizes). The application contained limited data comparing performance of delivery devices of the test and reference (Nasal Crom[®], Pharmacia and Upjohn, 5.2 mg/spray) products.

The Division of Bioequivalence (DBE) completed its review of this application on April 4, 1996. Based on that review, the firm was informed (letter date: April 16, 1996) that DBE had no further questions, and it was emphasized that the comments expressed in that letter were preliminary, which may be revised upon complete review of the application.

Though DBE completed its review previously, the "Office-Level" approval sheet was not prepared at that time. During preparation for the "Office-level" sign off, it was determined that the application was incomplete due to deficiencies in the Unit Dose (Uniformity of Dose), Priming and Repriming, and Droplet Size Distribution data. Therefore based on the 21 November 2000 amendment to the bioequivalency review, the firm was informed (letter date: 29 November 2000) of the following deficiencies:

1. *Unit Dose/Content Uniformity: The unit dose was based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from one lot of the test and reference products.*
2. *Priming, loss of prime, and tail off: Please submit data (based on a validated chromatographic/chemical assay) to support comparative performance of the test and reference products with regard to priming, loss of prime, and tail off.*

The reference listed drug's patient package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. **Droplet Size Distribution:** You determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sectors (Beginning, Middle and End). The test should be performed using 10 units of the test and reference products.

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

The firm has submitted the requested Unit Dose and Priming (December 21 amendment) and Droplet size distribution (11 December amendment) data. The 11 December amendment also contains Unit Dose and Priming data based on gravimetric measurements. The firm has been previously informed that such data were not acceptable to support bioequivalence of test and reference products. Therefore the following evaluation of the Priming/Repriming and Unit Dose data utilizes information based on an analysis given in the 21 December amendment.

Priming: The test and reference product units were actuated using InnovaSystem's automated actuation device designed for nasal sprays, with the following parameters:

| | |
|------------------|---------|
| Actuation force: | 5 kg |
| Dose time: | 25 msec |
| Return time: | 16 msec |
| Hold time: | 1 sec |
| Delay time: | 1 sec |

Priming characteristics of the test products were determined in terms of the amount of cromolyn sodium per spray beginning with the first actuation. The amount of drug in each actuation was determined using a validated assay.

Priming data for the 13-mL and 26-mL products are summarized on pages 21 and 22, vol. 41. Based on these data, both fill sizes of the test product deliver the labeled amount of cromolyn sodium by the 5th spray. Therefore the test products meet priming characteristics of the reference product.

Prime Retention/Loss of Prime: The reference listed drug's package insert states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before use. Therefore, the sponsor was requested to provide data supporting the sameness of prime retention characteristics of the test and reference products.

To determine prime retention characteristics the firm primed the test and reference products with five actuations. Another 100 actuations were wasted and the amount of drug present in spray #106 was determined. The units were left unused for 7 and 14 days. At the end of these periods, spray #107 was analyzed to determine the amount of drug.

Prime retention testing was performed on the 26-mL product only. As indicated in the 30 November Agency letter, separate testing for the 13-mL product may not be warranted because the 26- and 13-mL fill sizes use the same pump and actuator. The data showing 14-day prime retention are presented on page 39, vol. 4.1. These data indicate that, after the 14-day storage period, the test product delivered 90.6% of the label claim compared with 107.7% on day 1, a drop of 17.1%. One of the 10 test product bottles yielded 71.2% of label claim, which is outside the 80-120% of the label claim. After the same storage period, the reference product delivered 105.8% of the label claim compared with 114.4% on day 1. These data indicate that the prime retention characteristics of the test and reference products are *not* similar.

It is notable that the sponsor's testing of prime retention was not consistent with the reference product labeling. After the 14-day hold period, the next actuation (#107) was assayed for drug content, instead of wasting two sprays (as indicated in the RLD labeling) and analyzing the third spray (#109). Based on the prime retention data submitted by the firm, it is difficult to deduce whether the test product would have demonstrated same prime retention as the reference product, if the test was conducted consistent with the RLD labeling.

Tail Off: The sponsor determined comparative tail off characteristics of the test and reference products. Based on the data presented in vol. 4.1, pages 25-28, the test product delivers greater number of full medication doses. It starts tailing off at actuation #218 and the reference product tails off at actuation #201. The test product's tail off is no more erratic than that of the reference product. The tail off data are acceptable.

Unit Dose/Content Uniformity: In the 30 November 2000 letter, the sponsor was informed that unit dose data were requested only for 26-mL product, and separate testing for the 13-mL product was not requested because the 26- and 13-mL fill sizes use the same pump and actuator. Nonetheless, the priming data for the 13-mL product indicates that at the beginning of the product use (6th actuation), the test product delivers 104.6% of the label claim with a test/reference ratio of 0.96.

For the 26-mL product, this test was performed at the Beginning (actuators 6 and 7) and End of sectors (actuators 203 and 204 for Test, 199 and 200 for RLD) of the primed products. A summary of the unit dose data, and raw unit dose data are given on pages 24 and 33-36 (vol. 4.1), respectively. Based on these data the test/reference ratios for unit spray content at the beginning and end sectors were in the range of 0.96-0.97. None of the units (n=10) was outside 80-120% of the label claim. Variability (CV) of the test and reference products was in the range of 1.1-6.4% and 1.8-15.0%.

The unit dose data submitted by the sponsor are acceptable.

Droplet Size Distribution: The droplet size distribution of the test and reference products was studied using Malvern Mastersizer at Beginning (immediately after priming), Middle (actuators 97-105) and End (actuators 152-160) sectors of product life. The test was performed at three distances (3, 6 and 12 cm) from the orifice.

Droplet size distribution was characterized by D50 (median diameter) and SPAN. A summary of the relevant data is provided on pages 68 and 70 (vol. 5.1). Based on these data the test/reference ratios for D50 and SPAN were in the range of 1.00-1.13 and 1.09-1.19 respectively. For D50, variability (CV) of the test and reference products was in the range of 6.34-22.44% and 7.68- 20.44%, respectively. For SPAN, variability (CV) of the test and reference products was in the range of 8.02-18.03% and 7.63-17.17%, respectively. The sponsor did not provide raw data. Therefore, the reviewer could not determine statistical significance of the test-reference differences.

Based on the ratio of means, the test product's D50 and SPAN fall outside the 90-111% limits stipulated in the draft *Guidance for industry: Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action*. Therefore, the droplet size distribution data are not acceptable.

Device Comparability: In the 29 November letter, the firm was requested to provide information to establish comparability of the test and reference product devices. The sponsor submitted a technical drawing of the test product, with a statement that such information is not available for the reference product because of proprietary agreement between the supplier and the RLD manufacturer.

DBE acknowledges lack of availability of certain information due to the proprietary agreement. However, for both the 26- and 13-mL products, the sponsor should be able to determine the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter.

Comments

1. The priming and tail off data are acceptable.
2. The unit dose data are acceptable.
3. The prime retention (prime hold) data indicates that the prime retention characteristics of the test product after the 14-day storage period are not the same.
4. The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product.
5. For both the 26- and 13-mL products, the sponsor should provide information regarding the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter. In addition the firm should be requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.

Recommendation

The in vitro testing conducted by Barre-National (ALPHARMA) comparing its cromolyn sodium nasals sprays (5.2 mg/spray, 26- and 13-mL fill sizes) and the reference product (Nasalcrom® Pharmacia and Upjohn, 5.2 mg/spray) is incomplete due to deficiencies indicated in comments 3 - 5.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

Gur J.P. Singh 2/2/01

RD INITIALED S. NERURKAR

for FT INITIALED S. NERURKAR Moharawal Date 2/2/01

Concur: Dale P. Conner Date 2/2/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-800

APPLICANT: Barre-National
(ALPHARMA)

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL

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

1. **Unit Dose/Content Uniformity:** The unit dose was based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from one lot of the test and reference products.
2. **Priming, loss of prime, and tail off:** Please submit data (based on a validated chromatographic/chemical assay) to support comparative performance of then test and reference products with regard to priming, loss of prime, and tail off.

The reference listed drug's package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. **Droplet Size Distribution:** You determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sector (Beginning, Middle and End) sectors. The test should be performed using 10 units of the test and reference products.

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced

by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

Sincerely yours,

for 

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-800

APPLICANT: Barre-National
(ALPHARMA)

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL

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

1. **Unit Dose/Content Uniformity:** The unit dose was based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from one lot of the test and reference products.
2. **Priming, loss of prime, and tail off:** Please submit data (based on a validated chromatographic/chemical assay) to support comparative performance of then test and reference products with regard to priming, loss of prime, and tail off.

The reference listed drug's package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. **Droplet Size Distribution:** You determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sector (Beginning, Middle and End) sectors. The test should be performed using 10 units of the test and reference products.

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced

by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

Sincerely yours,


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

Cromolyn Sodium Nasal Solution Barre-National
(Nasal Spray)

40 mg/mL, 13 mL and 26 mL Baltimore, MD
nasal spray containers

ANDA #74800

Submission Date:

Reviewer: Moo Park

December 1, 1995

Filename: 74800W.D95

Review of two Waiver Requests

I. Objective

Review of Barre-National's waiver requests on two package sizes, 13 mL and 26 mL, of Cromolyn Sodium Nasal Solution, 40 mg/mL strength. Reference products are Fisons' Nasalcrom^R, 40 mg/mL, packaged in 13 mL and 26 mL nasal spray containers.

II. Background

Chemically, cromolyn sodium is the disodium salt of 1,3-bis (2-carboxychromon-5-yloxy)-2-hydroxypropane. The empirical formula is $C_{23}H_{14}Na_2O_{11}$.

- Pharmacologic Category: Mast cell stabilizer/antiallergic
- Therapeutic Category: Antiallergic
- Absorption: Cromolyn sodium is poorly absorbed from the gastrointestinal tract. After instillation, less than 7% of the total dose administered is absorbed and is rapidly excreted unchanged in the bile and urine. The remainder of the dose is expelled from the nose, or swallowed and excreted via the alimentary tract.
- Dosing: After priming the delivery system, each actuation of the unit delivers a metered spray containing 5.2 mg of cromolyn sodium. The contents of one bottle delivers at least 100 sprays (13 mL bottle) or 200 sprays (26 mL bottle).

III. Requirements for waiver

In vitro data showing the test and reference products are same:

- Formulation
- Performance of the finger pump: Volume per actuation, plume

geometry, spray pattern, droplet size, number of doses deliverable, etc.

IV. Formulation

Formulations for the test and reference products are identical. The test formulation is shown in Table 1.

Table 1. Test Formulation

| Ingredient | Amount |
|-----------------------|--------|
| Cromolyn sodium | |
| Benzalkonium chloride | |
| Edetate sodium | |
| Purified water | |
| Total | |

V. In Vitro Evaluation of finger pump

1. VOLUME (OR DOSE) DELIVERED

The average volume delivered for both the Nasalcrom[®] and Barre product in single and multiple actuation testing was 138 μ l per spray. The prescribed dose is one spray per nostril hence two sprays. Thus the volume of a typical dose based on this test would be 276 μ l. In the dose delivered through use life study, the average volumes delivered per dose were determined as 272 μ l for the 13 ml Nasalcrom[®], 271 μ l for the 26 ml Nasalcrom[®], 271 μ l for the 13 ml Barre product and 274 μ l for the 26 ml Barre product. These data indicate that the delivery from the device used on Barre product is equivalent to the Nasalcrom[®].

TABLE 2. VOLUME DELIVERED PER SINGLE ACTUATION

| <u>SAMPLE</u> | <u>AVERAGE</u> Target 130 μ L N=30 | <u>RSD</u> |
|------------------------|--|------------|
| Nasalcrom [®] | | |
| BARRE FORMULATION | | |

TABLE 3. VOLUME DELIVERED PER MULTIPLE ACTUATION

| <u>SAMPLE</u> | <u>AVERAGE</u> Target 130 μ L N=20 | <u>RSD</u> |
|------------------------|--|------------|
| Nasalcrom [®] | 138 μ L | 1.54% |
| BARRE FORMULATION | 138 μ L | 1.35% |

TABLE 4. CROMOLYN SODIUM DELIVERED PER SINGLE ACTUATION

| <u>SAMPLE</u> | <u>AVERAGE</u> Target = 5.2 mg N = 30 | <u>RSD</u> |
|------------------------|---|------------|
| Nasalcrom [®] | 5.45 mg | 2.71% |
| BARRE Product | 5.56 mg | 1.89% |

TABLE 5. CROMOLYN SODIUM DELIVERED PER MULTIPLE ACTUATION

| <u>SAMPLE</u> | <u>AVERAGE</u> Target = 5.2 mg N = 20 | <u>RSD</u> |
|------------------------|---|------------|
| Nasalcrom [®] | 5.46 mg | 2.31% |
| BARRE FORMULATION | 5.58 mg | 1.28% |

2. DOSE DELIVERED THROUGH THE USE LIFE OF THE UNIT

Ten samples for both bottle sizes of the Cromolyn Sodium Nasal Solution, USP (Barre formulation lot# PH5546) utilizing three lots of Valois VP3/140F pumps (lot#'s: 13 ml - 018828, 018328, 018007 & 26 ml - 018829, 018329, 018008) were evaluated. In addition, ten samples for both bottle sizes of the Nasalcrom[®] using three separate lots (lot#'s: 13 ml - ALF5E, ALF503E, ALF504E & 26 ml - AKE507E, AKE503G, AKE48D) were evaluated in this study.

Each set of two sprays represents one dose - 1 spray per nostril. For the 13 ml bottle size, the claimed use life is 100 sprays (or 50 doses) for the 26 ml the claim is 200 sprays (100 doses). From the measured spray weights, the quantity of Cromolyn Sodium

delivered was calculated in the same fashion as outlined for the Volume (or dose) Delivered. A suitable dose of two sprays was considered 10.4 mg Cromolyn Sodium \pm 33%. Therefore, it was expected that the product would deliver 50 (13 ml size) or 100 (26 ml size) consecutive doses after priming within the range of 10.4 mg Cromolyn Sodium \pm 33% (limits 7.0 mg to 13.8 mg).

From Figures 1 through 4, it is apparent that neither bottle size for both the Nasalcrom[®] and Barre product met the criteria of delivering 10.4 mg \pm 33% Cromolyn Sodium per dose during the expected life of the product.

13 ml Bottle Size

Figure 1. Dose Delivered Through Use Life of Nasalcrom®
Target = 10.4 mg (limits 7.0 to 13.8 mg)

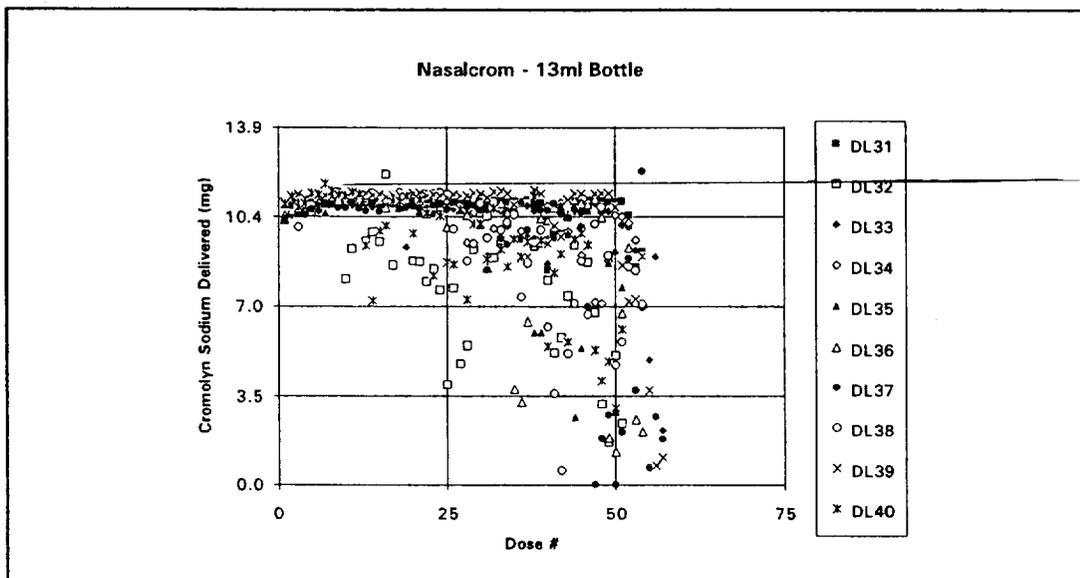
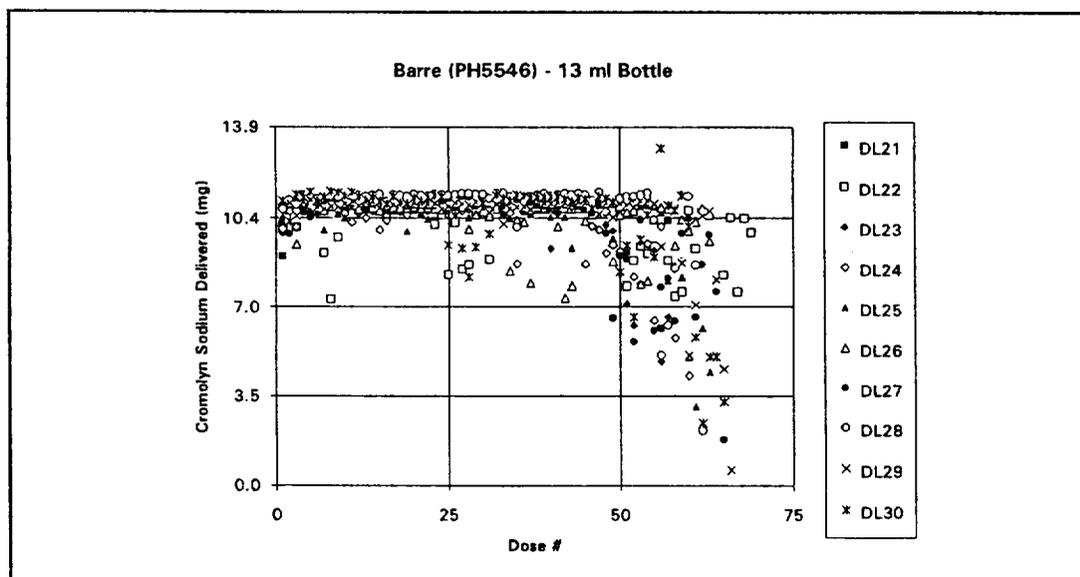


Figure 2. Dose Delivered Through Use Life of Barre Product
Target = 10.4 mg (limits 7.0 to 13.8 mg)



26 ml Bottle Size

Figure 3. Dose Delivered Through Use Life of Nasalcrom®
Target = 10.4 mg (limits 7.0 to 13.8 mg)

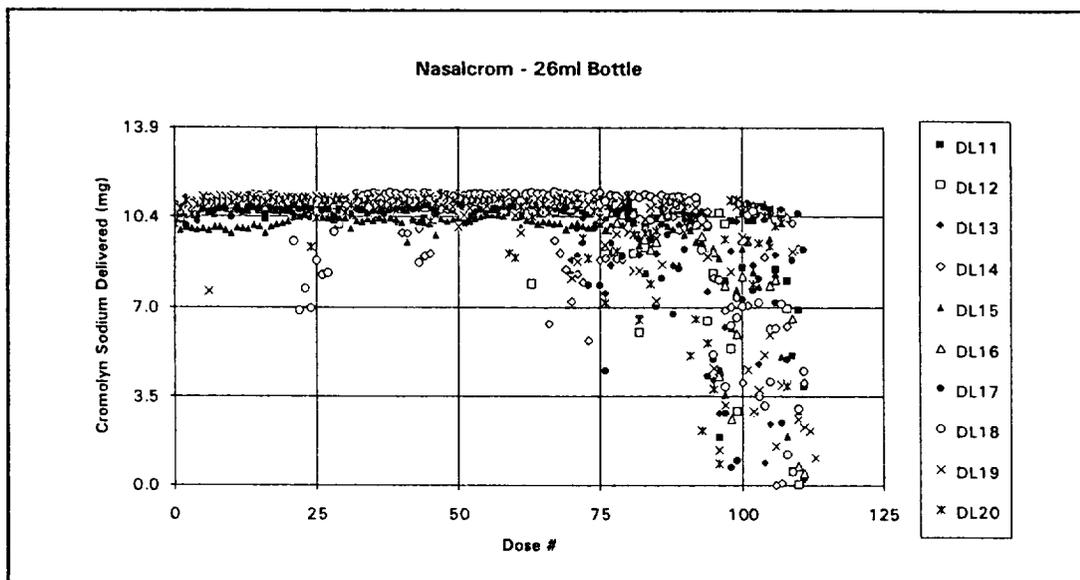
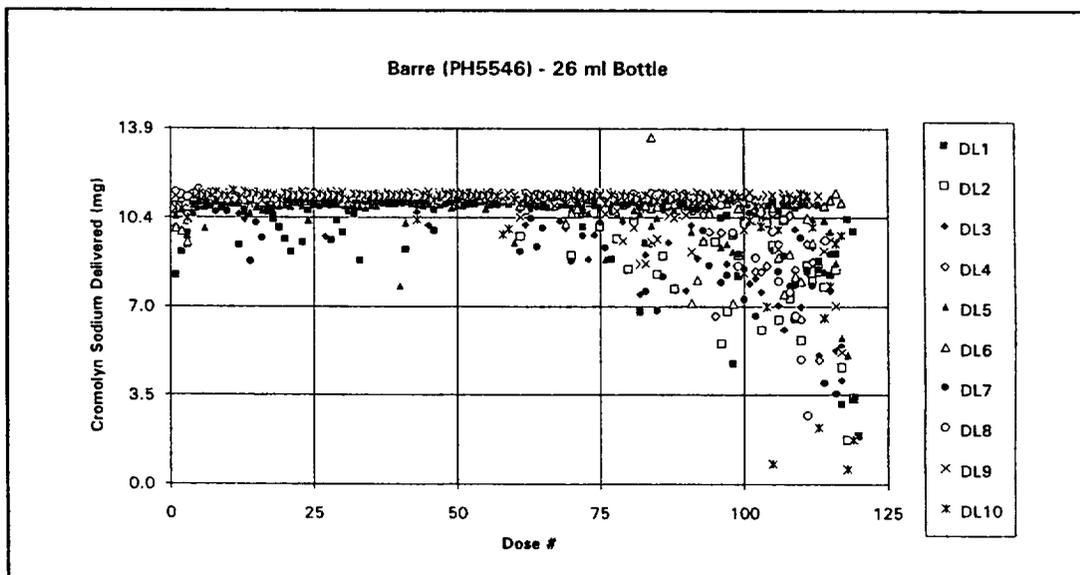


Figure 4. Dose Delivered Through Use Life of Barre Product
Target = 10.4 mg (limits 7.0 to 13.8 mg)



A comparison of the mean volume of spray delivered from each bottle size per dose is shown in Table 6. The mean volume was calculated using only the first 25 doses in the 13 ml size and the first 65 doses in the 26 ml size.

Table 6. Cumulative Mean Volume Delivered per Dose

| | Nasalchrom® | | Barre Product | |
|------------------|-------------|-------------|---------------|-------------|
| | 13 ml | 26 ml | 13 ml | 26 ml |
| Mean Volume/dose | 272 μ l | 271 μ l | 271 μ l | 274 μ l |
| %RSD | 3.90% | 1.74% | 2.50% | 2.03% |

The mean volume delivered per dose by the Barre product in the 13 ml bottle size was 0.4% lower than the Nasalchrom®. The 26 ml bottle size of the Barre product delivered 1.1% more volume per dose than the Nasalchrom®.

The delivery of the Barre product in both bottle sizes is equivalent to the Nasalchrom® for approximately the first half of the use life. Beyond that point, the Barre product consistently delivers the expected dose while the Nasalchrom® starts to exhibit an increase in the number of low doses. The performance of the pumps used on both bottle sizes of the Barre product is equivalent to those of the reference product.

3. DROPLET SIZE DISTRIBUTION

The light scattering device was used to measure the droplet size of this fine mist. The measured median diameter, $d(0.5)$, the % less than $9.48 \mu\text{m}$ and the computed span, were used to characterize the droplet size distribution produced by the nasal spray pumps. The span is a measure of the width of the distribution calculated from the data at the 10th, 50th and 90th percentiles of the volume distribution. The equation is shown below:

$$\text{SPAN} = [d(0.9) - d(0.1)] / d(0.5)$$

Ten samples of the Barre formulation with three lots of the ; pump and ten samples of Nasalchrom® from three separate lots were evaluated in this study. The test heights employed were 3, 6 and 12 cm.

The average median droplet size distribution of the Barre product was found to be slightly smaller than the Nasalchrom® as measured by the light scattering instrument. These differences

were not significant. The reference and Barre products are equivalent. Since the droplets will only travel a short distance before impaction, median droplet size is not a critical parameter. The fraction below approximately 9 microns is of greater interest since this represents the portion of the dose which could potentially become entrained in the airstream and not be available for nasal administration. The results showed both the Nasalcrom[®] and Barre product only produce about 1 to 1.5% of the dose below 9.48 microns. The Impactor (without preseparator) selectively admits particles less than 9 microns based on their mass median aerodynamic diameter (MMAD).

The median diameter of the droplets generated by a nasal spray actuator is much larger than the size appropriate for the

Therefore, only a very small portion of the sample will actually be evaluated in the test. The majority of the Cromolyn Sodium, approximately 99%, for both products was recovered in Fraction A. Fraction A has a cutoff diameter of greater than 9 microns. Thus these results indicate that the majority of the spray droplets are larger than 9 microns in diameter and that the drug will be deposited in the desired location, the nasal cavity. These results agreed closely with the Impactor results in which approximately 1% of the dose was found to be below 9 microns. Thus the Barre product and the Nasalcrom[®] are equivalent in terms of the droplet size distribution.

TABLE 7. SUMMARY OF DROPLET SIZE RESULTS BY MALVERN

| DETERMINATION OF DROPLET SIZE BY MALVERN | | | | | | | |
|--|-------------------|----------------------------|------|------|-------|------------------------|------|
| SAMPLE | Test Height cm | d(0.5) - (μm) | | Span | | % < 9.48 μm | |
| | | Avg | %RSD | Avg | %RSD | Avg | %RSD |
| Nasalacrom [®] | 3 | 56.1 | 9.57 | 1.96 | 12.34 | 1.33 | 13.4 |
| Barre Product | | 51.8 | 9.66 | 2.08 | 16.8 | 1.56 | 21.5 |
| Nasalacrom [®] | 6 | 50.2 | 7.62 | 1.90 | 47.4 | 1.52 | 10.4 |
| Barre Product | | 48.8 | 5.74 | 1.32 | 9.03 | 1.62 | 13.6 |
| Nasalacrom [®] | 12 | 62.3 | 3.84 | 1.12 | 6.93 | 1.04 | 15.8 |
| Barre Product | | 60.2 | 5.33 | 1.05 | 12.1 | 1.06 | 25.6 |

4. SHAPE OF THE SPRAY PLUME

The actuations were captured on high speed video film. The film was then edited to slow motion and frames of the spray plumes at their apex were selected. Photographs of the selected frames were developed and used to make measurements of the spray plume. Two measurements, the longest vertical distance (LVD) and the widest horizontal distance (WHD), were taken from the photographs. A measurement of the grid was also performed and used to correct the height and width for the reduction of size that occurred during videotaping and photograph production.

In both the spray pattern testing and plume geometry testing, negligible differences were noted. In general the Barre product did not produce as wide of a plume as the brand. These differences were not significant especially in light of the narrow confines of the nasal cavity. Thus the Barre product and the Nasalacrom[®] are equivalent in terms of the shape of the spray plume.

Table 8 represents the Nasalacrom[®] and Barre product averages and relative standard deviations (RSD) for the shortest and longest diameters at the three test heights. The limit represents a +/- 25% range around the mean diameters of the Nasalacrom[®] product.

Equivalency between the Nasalcrom® and the Barre product can be established if the averages for the shortest and longest diameter for the Barre product are within this range.

TABLE 8. Spray Pattern Analysis

| SPRAY PATTERN ANALYSIS | | | | | | | |
|------------------------|-------------|---------------------|-----|-----|---------------------|-----|-----|
| SAMPLE | Test Ht. cm | S _D (mm) | | | L _D (mm) | | |
| | | Limit | Avg | RSD | Limit | Avg | RSD |
| Nasalcrom® | 2.5 | 41-68 | 55 | 5% | 50-83 | 66 | 8% |
| Barre Product | | | 49 | 11% | | 58 | 8% |
| | | | | | | | |
| Nasalcrom® | 5.0 | 56-94 | 75 | 6% | 67-112 | 90 | 4% |
| Barre Product | | | 72 | 6% | | 85 | 4% |
| | | | | | | | |
| Nasalcrom® | 7.5 | 53-88 | 70 | 11% | 68-113 | 90 | 10% |
| Barre Product | | | 81 | 13% | | 101 | 10% |

The average results for the Longest Vertical Distance (LVD) and Widest Horizontal Distance (WHD) in millimeters are presented in Table 9.

Table 9. Analysis Of Plume Geometry

| | Nasalcrom® | | Barre Product | |
|--------------|------------|-------|---------------|-------|
| | LVD | WHD | LVD | WHD |
| Average (mm) | 444 | 196 | 487 | 180 |
| %RSD | 4.30% | 9.23% | 3.22% | 8.98% |

VI. Comments

1. Volume (or dose) delivered: The average volume delivered for both the Nasalcrom[®] and Barre product in single and multiple actuation testing was 138 μ l per spray (equivalent to 5.5 mg cromolyn sodium). The delivery from the device used on Barre product is equivalent to the Nasalcrom[®].
2. Droplet size distribution: Median diameters ranged from 49 to 62 micrometer with comparable distributions for the test and reference products.
3. Spray pattern and flume geometry are comparable for the test and reference products.
4. The formulations for the test and reference products are identical.
5. Waiver of *in vivo* bioequivalence study requirements is granted for the test product.

VII. Deficiency

None.

VIII. Recommendation

The Division of Bioequivalence agrees that the information submitted by Barre-National demonstrate that Cromolyn Sodium Nasal Solution, 40 mg/mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Fisons' Nasalcrom[®] Nasal Solution, 40 mg/mL.

The firm should be informed of the recommendation.


 Moo Park, Ph.D.
 Chemist, Review Branch III
 Division of Bioequivalence

RD INITIALED RMHATRE
 FT INITIALED RMHATRE

Ramant M. Mhatre 3/26/96

Concur: _____



Date: _____

4/4/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

File history:

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-800

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-800

FIRM: Alparma
Attention: Martin Levy, Director of
Regulatory Affairs
Research and Development Center
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

DOSAGE FORM: Nasal Spray

STRENGTH: 40 mg/mL, 5.2 mg/spray, 13 mL (100 sprays)
and 26 mL (200 sprays)

DRUG: Cromolyn Sodium

CGMP STATEMENT/EIR UPDATED STATUS: An EER has been issued for the indicated firms. An acceptable EER was received from the Office of Compliance for the newly constructed Alparma manufacturing area in the firm's existing facility, and the Profarmaco drug substance manufacturing facility on 10/13/00.

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:

Alparma
7205 Windsor Blvd
Baltimore, MD 21224

Alparma will obtain Cromolyn Sodium drug substance manufactured by:

. has provided the appropriate cGMP compliance statement.

A LOA dated October 5, 1993 authorized B/N to reference . The LOA was included in the DMF and a copy is present in the ANDA submission. The DMF was most recently reviewed on 9/20/99 by K. Furnkranz of HFD-

625 as a result of a DMF update. The DMF was found acceptable at that time.

BIOEQUIVALENCY STATUS: The firm requested a waiver from performing a bioavailability / bioequivalence study due to the quantitative and qualitative sameness of their product with Nasalcrom®; Fisons. The Division of Bioequivalence has found the firm's formulation Q1 and Q2 the same as the reference product. The in-vitro testing conducted by Barre-National (Alpharma), comparing its cromolyn sodium nasal sprays (5.2 mg/spray, 26- and 13-mL fill sizes) and the reference product (Nasalcrom® Pharmacia and Upjohn, 5.2 mg/spray) has been found to be acceptable to the Division of Bioequivalence. In terms of dose delivered per actuation, the size shape and droplet size distribution of the spray, the test product's performance is similar to that of the reference product. Therefore the Division of Bioequivalence deems the test product to be equivalent to the reference product in dose delivery and performance of the delivery device.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Method Validation by the District Laboratory is not required for the approval of the application. The drug substance and drug product are USP.

Alpharma has adequately validated the method for Cromolyn Sodium and Benzalkonium Chloride in the nasal spray, and has determined the methods to be adequate for their intended use. The methods will be considered an in-house method. The USP method will be the regulatory method (refer to the Chemistry Review #1 for additional information).

Intentional forced-degradation studies were performed on the drug product as part of the analytical methods validation. High temperature, light, acid, base and peroxide stress testing was performed (refer to the Chemistry Review #1 in Vol 1.1 for full details).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

The Cromolyn Sodium Nasal solution will be marketed in 13 mL and 26 mL fill sizes. The container/closure/delivery system consists of a metered dose spray pump with a external Spray Actuator, and a white cylinder bottle. Full

information on the c/c system, including the identity, composition and manufacturer of each component, is contained in Chemistry Review #1 and Chemistry Review #7).

* **LABELING: SATISFACTORY.** Labeling was found satisfactory as per the 5/18/99 labeling review/approval summary of Theresa Watkins (Vol. 4.1).

STERILIZATION VALIDATION (IF APPLICABLE): N/A. Alpharma constructed a Class environment for the manufacture of Nasal Spray drug products. The filter system used by Alpharma is not intended to be a microbial retention filter system. Alpharma has established bioburden limits for the bulk solution prior to filtration (in addition to limits for the finished packaged product and stability limits). The tests and limits have been incorporated into the enclosed Master Specifications Finished Product document. Alpharma has demonstrated that the bioburden levels have been reduced as a result of the filtration process. Adequate preservation of the drug product at 50% BAC content was demonstrated.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):

2 exhibit batches (Lot #VP0774 and VP0775) of each were manufactured on 12/11/00 and 12/14/00. They were filled into a 26 mL and a 13 mL bottle, respectively. Complete batch records, finished product release data and stability data were included (refer to pp. 45 - 125 of the 6/15/01 ANDA Amendment for the batch records and certificates of analysis).

Alpharma previously submitted a blank batch record for a r production batch. Alpharma has established a maximum time between final filtration and packaging of 5 days.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?):

The exhibit batches (VP0774 and VP0775) manufactured to support this application were used in the In Vitro bioequivalence studies as well as the stability studies.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The production batches will be manufactured utilizing the same manufacturing process as used for the exhibit batch.

*

M. J. Smith

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

| | | |
|---|--|-----------------------------------|
| Application: ANDA 74800/000 | Priority: | Org Code: 600 |
| Stamp: 04-DEC-1995 Regulatory Due: | Action Goal: | District Goal: 04-FEB-1997 |
| Applicant: ALPHARMA USPD | Brand Name: | |
| 333 CASSELL DR STE 3500 | Established Name: CROMOLYN SODIUM | |
| BALTIMORE, MD 21224 | Generic Name: | |
| | Dosage Form: SOL (SOLUTION) | |
| | Strength: 4% NASAL | |
| <hr/> | | |
| FDA Contacts: M. DILLAHUNT (HFD-613) | 301-827-5846 | , Project Manager |
| K. FURNKRANZ (HFD-625) | 301-827-5848 | , Review Chemist |
| M. SMELA JR (HFD-625) | 301-827-5848 | , Team Leader |

Overall Recommendation:

WITHHOLD on 21-DEC-1999 by S. FERGUSON (HFD-324) 301-827-0062

WITHHOLD on 02-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

WITHHOLD on 16-JUN-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-DEC-1999**
Decision: **WITHHOLD**
Reason: **FIRM NOT READY**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-800

FIRM: Alpharma
Attention: Martin Levy, Director of Regulatory Affairs
Research and Development Center
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

DOSAGE FORM: Nasal Spray

STRENGTH: 40 mg/mL

DRUG: Cromolyn Sodium

CGMP STATEMENT/EIR UPDATED STATUS: An EER has been issued for the indicated firms. EER is pending for Alpharma (firm was not ready for the inspection when it was previously scheduled)

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:

Alpharma
7205 Windsor Blvd
Baltimore, MD 21224

Alpharma will obtain Cromolyn Sodium drug substance manufactured by:

J.R.L. has provided the appropriate cGMP compliance statement.

A LOA dated October 5, 1993 authorized B/N to reference [redacted]'s DMF. The LOA was included in the DMF and a copy is present in the ANDA submission. The DMF was most recently reviewed on 9/20/99 by K. Furnkranz of HFD-625 as a result of a DMF update. The DMF was found acceptable at that time.

BIOEQUIVALENCY STATUS: The firm requested a waiver from performing a bioavailability / bioequivalence study due to the quantitative and qualitative similarity of their product with Nasalcrom®; Fisons. The Division of Bioequivalence had no further questions after the 4/16/96 review.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Method validation by the District Laboratory is not required for the approval of the application. The drug substance and drug product are USP.

Alpharma has adequately validated the method for Cromolyn Sodium and Benzalkonium Chloride in the nasal spray, and has determined the methods to be adequate for their intended use. The methods will be considered an in-house method. The USP method will be the regulatory method (refer to the Chemistry Review #1 for additional information).

Intentional forced-degradation studies were performed on the drug product as part of the analytical methods validation. High temperature, light, acid, base and peroxide stress testing was performed (refer to the Chemistry Review #1 in Vol 1.1 for full details).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

The Cromolyn Sodium Nasal solution will be marketed in 13 mL and 26 mL fill sizes. The container/closure/delivery system consists of a metered dose spray pump inserted into a white cylinder bottle (full information on the c/c system, including the identity, composition and manufacturer of each component, is contained in Chemistry Review #1).

LABELING: SATISFACTORY. Labeling was found satisfactory as per the 5/18/99 labeling review/approval summary of Theresa Watkins (Vol. 4.1).

STERILIZATION VALIDATION (IF APPLICABLE): N/A. Alpharma constructed a Class environment for the manufacture of Nasal Spray drug products. The filter system used by Alpharma is not intended to be a microbial retention filter system. Alpharma has established bioburden limits for the bulk solution prior to filtration (in addition to limits for the finished packaged product and stability limits). The tests and limits have been incorporated into the enclosed Master Specifications Finished Product document. Alpharma has demonstrated that the bioburden levels have been reduced as a result of the filtration process. Adequate preservation of the drug product at 50% BAC content was demonstrated.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):

An exhibit batch #PN7828 of was manufactured on 10/7/97. The bulk batch was filled into the two container sizes of 13 mL (batch #653701) and 26 mL (batch #653702). The batch records are included on pp. 242 - 341 of the 5/6/98 ANDA Amendment.

Alpharma also submitted a blank batch record for a liter production batch. Alpharma has established a maximum time between final filtration and packaging of 5 days.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY

MANUFACTURED VIA SAME PROCESS?): The exhibit batch manufactured to support this application was used in the In Vitro bioequivalence studies as well as the stability studies.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? The production batches will be manufactured utilizing the same manufacturing process as used for the exhibit batch.

cc:

Endc

12/6/99
Smela 12/6/99
doc

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

ANDA Number: **74-800** Date of Submission: **May 6, 1998**

Applicant's Name: **Alpharma USPD**

Established Name: **Cromolyn Sodium Nasal Solution USP,
4% (40 mg/mL)**

Labeling Deficiencies:

1. CONTAINER (13 mL and 26 mL)

Satisfactory in printers proof.

2. CARTON (1 x 13 mL and 1 x 26 mL)

Delete the "Non-drowsy" red triangle that appears on the main panel.

3. INSERT

Satisfactory in printers proof.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

A handwritten signature in black ink, appearing to read "John J. Phillips", is written over a horizontal line.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74-800

CORRESPONDENCE



U.S. Pharmaceuticals Division

July 16, 2001

TELEPHONE AMENDMENT TO A PENDING APPLICATION

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

ORIG AMENDMENT
N/AF

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

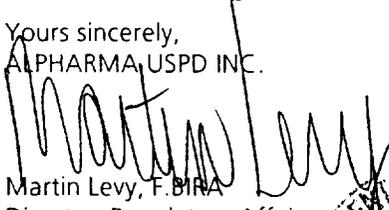
Dear Mr. Beuhler:

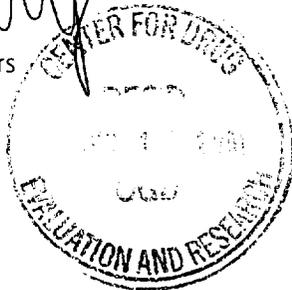
Further to our discussions with FDA managers, specifically, Mr. Bob West and Mr. John Grace, Alpharma, USPD Inc. was made aware of revised innovator labeling for this product. We have made the necessary changes to our labeling and forward it for substantive review.

Alpharma notes that Mr. West indicated that mock-ups for the labeling would be acceptable.

For ease of reference, contact the undersigned at 410-277-1742 or by fax at 410-277-1800.

Yours sincerely,
ALPHARMA, USPD INC.


Martin Levy, F.B.I.R.A.
Director, Regulatory Affairs
Enclosures



Alpharma USPD Inc.

Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Tel (410) 298-1000
Fax (410) 277-1810

July 6, 2001

TELEPHONE AMENDMENT TO A PENDING APPLICATION

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

ORIG AMENDMENT
N/AM

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review, a telephone amendment. Specifically, we have submitted documentation that was requested by the Agency (Mr. Mike Smela, Team Leader) in our conversation on June 28, 2001.

We have included the data for the three-month time point as requested.

For ease of reference, contact Martin Levy, Director of Regulatory Affairs at 410-277-1742 or by fax at 410-277-1800.

Yours sincerely,
ALPHARMA USPD INC.



Ronald L. Nedich, Ph.D.
Vice President, R&D and Regulatory Affairs

RN/fm
Enclosures





June 15, 2001

MINOR AMENDMENT TO A PENDING APPLICATION

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

N/A

ORIG AMENDMENT

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review, a minor amendment. Specifically, we have submitted documentation that was requested by the Agency (Mr. Gary Buehler, R.Ph., Acting Director) in our conversation on May 10, 2001.

The applicant has made a change to the pump actuator on our Cromolyn Sodium Nasal product. We have included the accelerated stability data for the new actuator and the supporting documentation as required.

For ease of reference, contact Martin Levy, Director of Regulatory Affairs at 410-277-1742 or by fax at 410-277-1800.

Yours sincerely,
ALPHARMA USPD INC.

Ronald L. Nedich, Ph.D.
Vice President, R&D and Regulatory Affairs

RN/fm
Enclosures



Correspondence (c)

division pharmacie

Valois 

April 11th, 2001

NEW CORRESP

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Gary Buehler, Acting Director

RE: ANDA 74-800 / Cromolyn Sodium Nasal Solution
Drug Product Applicant: ALPHARMA USPD Inc.

Dear Mr. Buehler,

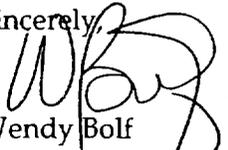
Our client, Apharma USPD Inc., has requested that we forward this communication to you concerning their intention to use our actuator as a packaging component for the aforementioned product.

Please find attached Valois' submission which explains the difference between the current and proposed actuator. Please note that both actuators are described in the same . Our customer has received a letter of authorisation for this DMF.

We understand that the this will remain confidential and cannot be disclosed under FOI.

Should you have any questions, please do not hesitate to contact either myself in France, or Alex Theodorakis at our Connecticut office at 203-661-5455 (fax: 203 622-2367).

Sincerely,


Wendy Bolf
Manager, Regulatory Affairs
VALOIS PHARM
Le Vaudreuil, FRANCE



Handwritten initials and date: WB 6-11-01

May 8, 2001

TELEPHONE AMENDMENT

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

NDA ORIG AMENDMENT
N/AB

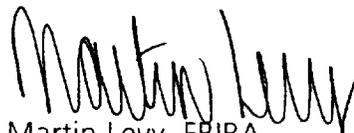
Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a telephone amendment. Specifically, we have submitted documentation that was requested by Dr. Gur Singh in our conversation on May 7, 2001. This documentation supplements our application and specifically our amendment of April 23, 2001.

For ease of reference, the undersigned may be contacted at 410-277-1742.

Yours sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs

ML/fm
Enclosures



April 23, 2001

TELEPHONE AMENDMENT

MLB

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

N/AB
~~GEN AMENDMENT~~

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a telephone amendment. Specifically, we have submitted documentation and data that was requested by Dr. Gur Singh in our conversation on April 13, 2001. This documentation supplements our application and specifically our amendment of April 10, 2001.

For ease of reference, the undersigned may be contacted at 410-277-1742.

Yours sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs

ML/fm
Enclosures



April 10, 2001

TELEPHONE AMENDMENT

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

NDA ORIG AMENDMENT
N/AB

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

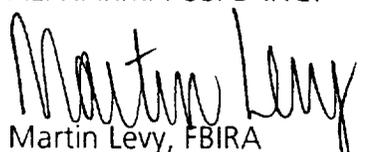
Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a telephone amendment. Specifically, we have submitted additional bioequivalency data to support the revision of our container/closure system. Reference is made to the March 23, 2001 teleconference with the Agency (Dr. Lizzie Sanchez, Dr. Shriniwas Nerurkar, Dr. Gur Singh, and Dr. Neena Nwaba) which outlined the data necessary to support approval of Cromolyn Sodium Nasal Solution jacket.

Alpharma has included the bioequivalency data requested by the Agency.

For ease of reference, the undersigned may be contacted at 410-277-1742 should you have any questions concerning our responses.

Sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs



ML/fm
Enclosures



U.S. Pharmaceuticals Division

April 4, 2001

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

NEW DRUG AMENDMENT

AA

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL
Proposal for Approval

Dear Mr. Buehler:

Reference is made to our original Abbreviated New Drug Application, which was filed on December 1, 1995, and the subsequent amendments to this file. In addition, we reference various telephone conversations with Mr. Robert West, the Division of Bioequivalence and the Division of Chemistry.

Alpharma USPD Inc. started its development program with an actuator that was proposed by the pump vendor, [redacted] actuator supplied comparable results to the innovator actuator [redacted] as demonstrated by *in vitro* studies performed by Alpharma in 1995 (see generally: Study Protocol Number 155BR-003R). Through the years, [redacted] manufactured this actuator repeatedly and unfortunately with great variation leading in 2001 to an actuator that had different outcomes for droplet size. Alpharma scientists and management agreed to replace the [redacted] actuator with the [redacted] actuator (the RLD's approved actuator) for testing and for commercializing purposes, thereby assuring the "sameness" of our products.

In March 2001, we brought this understanding to the attention of the Divisions of Bioequivalence and Chemistry and requested their guidance on the additional testing that would be required. The Division of Bioequivalence requested three additional tests (unit life, droplet size and spray pattern) while Chemistry requested testing related to resin changes, if any, and 3 months accelerated and room temperature stability. Alpharma has made a new batch and conducted the requisite *in vitro* tests and has placed the product on stability.

Alpharma wishes to bring to your attention the absence of change that is occurring with this innocuous modification to our product:

1. The formulation remains unchanged. This is a true solution composed of water, a preservative and Cromolyn Sodium.
2. The container/closure system remains unchanged except for the placement of a different actuator. The difference between the actuators [redacted] is the shape of the actuator head.
3. The resins of all components remain the unchanged except for the external insert, which changes by the inclusion of Acetal resin, and the exclusion of [redacted] resin. A "prior approval" letter (resin/part has been previously approved by CDER for a metered dose inhaler) will be filed to our file on April 10, 2001 by Valois directly.

As you can see there is essentially no chance for the stability of the product to be impacted by the change in the actuator.

With this information in mind, coupled with the Agency missteps associated with this application, Alpharma proposes to file an amendment with one-month accelerated and room temperature

Alpharma USPD Inc.

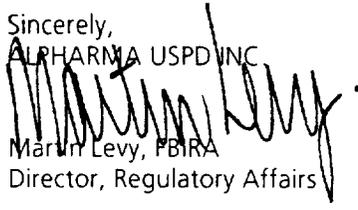
Research & Development Center Tel (410) 298-1000
The Johns Hopkins Bayview Center Fax (410) 277-1810
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

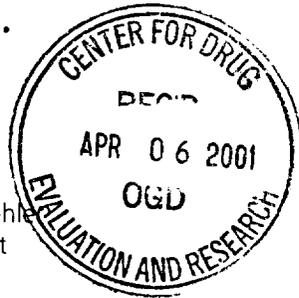


stability data as well as responses to the Division of Bioequivalence's questions in order to gain approval. The two additional months will be submitted to the ANDA as they become available. Alpharma seeks your approval based on the one-month data and commits to withdraw from the market any and all product should there be a problem with the stability data. In consideration that the innovator is using the precise actuator proposed by Alpharma, the acceptable in vitro testing, and the lack of significant change of any contact surface of the container closure system, we do not foresee any difficulties.

Alpharma understands that the Agency doesn't routinely make decisions based on economic parameters, however, Alpharma has entered into an agreement with a large branded pharmaceutical interest. Under the agreement, Alpharma will sell very large volumes of this product for sale under the branded firm's name for cold preparations. Our agreement originally established March 30th as the deadline for Alpharma's approval. This date has been extended until May. In our opinion, this unnecessary delay in our approval will negatively affect the agreement, which will directly and severely affect Alpharma's fiscal health.

For ease of reference, the undersigned may be contacted at 410-277-1742 should you have any questions concerning this letter.

Sincerely,
ALPHARMA USPD INC

Martin Levy, PBIRA
Director, Regulatory Affairs



Cc By Fax: Mr. Gary Buehle
Mr. Bob West

February 27, 2001

RESPONSE TO A MINOR ACTION LETTER TO A PENDING FILE

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Director

ORIG AMENDMENT

N/AB

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a minor amendment to a pending file. Specifically, we have submitted new bioequivalency data to support approval of our Cromolyn Sodium Nasal Solution jacket. Reference is made to the Agency's letter of February 5, 2001 (attached) and our abbreviated new drug application dated December 1, 1995.

Alpharma has responded to each question posed by the Agency in the order it was presented in the aforementioned letter.

For ease of reference, the undersigned may be contacted at 410-277-1742 should you have any questions concerning our responses.

Sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs



ML/fm
Enclosures

March 13, 2001

TELECONFERENCE PARTICIPANTS UNDER MAPP 4512.1

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Neena Nwaba, Ph.D., Project Manager, BE

RE: REQUEST FOR TELECONFERENCE ON MARCH 16, 2001

Dear Dr. Nwaba:

Reference is made to the Agency request for a teleconference on March 16, 2001 at 9:15 am to discuss ANDA 74-800. Alpharma is pleased to speak with the Agency to clarify its February 28th Minor amendment.

Present for Alpharma USPD Inc. will be:

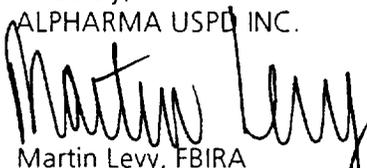
[Handwritten marks]

We look forward to speaking with you and your colleagues on March 16. Please ring my office (410-277-1742) and you will be transferred to Alpharma participants.

If you should require any additional information regarding this request, please do not hesitate to contact me at (410) 277-1742 or by fax at (410) 277-1800.

1810

Sincerely,
ALPHARMA USPD INC.

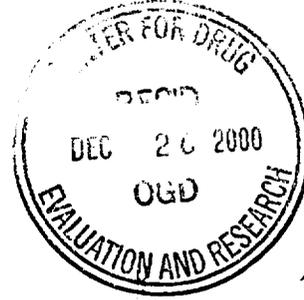

Martin Levy, FBIRA
Director, Regulatory Affairs

December 21, 2000

**MINOR AMENDMENT TO A PENDING APPLICATION
EXPEDITED REVIEW REQUESTED**

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

ORIG AMENDMENT
N/AM



Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

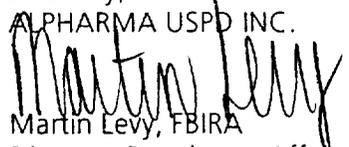
Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a minor amendment to our pending application. Reference is made to the Agency's letter of November 30, 2000 (attached) and our abbreviated new drug application dated December 1, 1995.

As we noted in our December 11 submission, the report, "Pump Performance: Including Pump Priming, Pump Prime Hold, Unit Spray Content through Life and Fall Off Studies" is attached at this time for Agency review.

We would appreciate if the conditions that held for the December 11 submission apply for this document.

For ease of reference, the undersigned may be contacted at 410-277-1742 should you have any questions concerning our responses.

Sincerely,
ALPHARMA USPD INC.

Martin Levy, FBIRA
Director, Regulatory Affairs

Handwritten initials and date: ML 12/29/00



December 11, 2000

**MINOR AMENDMENT TO A PENDING APPLICATION
EXPEDITED REVIEW REQUESTED**

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Gary Buehler, R.Ph., Acting Director

ORIG AMENDMENT
N/AM

Re: **ANDA #74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Beuhler:

Alpharma, USPD Inc. forwards for review by your BE team, a minor amendment to our pending application. Reference is made to the Agency's letter of November 30, 2000 (attached) and our abbreviated new drug application dated December 1, 1995.

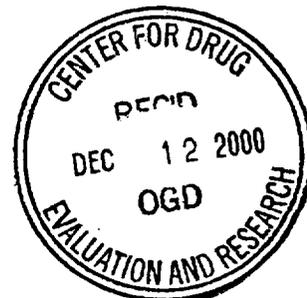
Alpharma had a communication on November 29 with Mr. Bob West concerning our jacket and it is our understanding that the BE team had undertaken a re-review of the bioequivalency information. It was our mutual undertaking that information forwarded to this application as a result of an Agency BE informational letter would be reviewed in an expedited manner, in keeping with the OGD Policy and Procedure guide 18-90. It should be noted, as we discussed with Mr. West, that there is an extraordinary hardship on the applicant as a result of the re-review of the file, considering, as we understand, the file has been in the approval matrix for many months and is approaching final approval.

For ease of reference, the undersigned may be contacted at 410-277-1742 should you have any questions concerning our responses.

Sincerely,
ALPHARMA USPD INC.

Martin Levy
Martin Levy, FBIRA
Director, Regulatory Affairs

ML/fm
Enclosures



Alpharma USPD Inc.

Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Tel (410) 298-1000
Fax (410) 277-1810

ML
12/1

NOV 21 1995

FILE COPY

Cromolyn Sodium

Nasal Solution (26- & 13-mL Sizes)

40 mg/mL (5.2 mg/ Actuation)

ANDA #74-800

Reviewer: Gur J.P. Singh

File name: 74800A.D95

Barre-National (ALPHARMA)

Cassel Drive

Baltimore, MD

Submission Date: Dec. 1, 1995

An Amendment to a Bioequivalency Review

Barre-National submitted this application on December 1, 1995. The application contained a request for waiver of in vivo bioequivalence study requirements for its cromolyn sodium 5.2 mg/actuation nasal sprays (26- and 13-mL fill sizes). The application contained limited data comparing performance of delivery devices of the test and reference (Nasalcrom® Pharmacia and Upjohn, 5.2 mg/spray) products.

The Division of Bioequivalence (DBE) completed its review of this application on April 4, 1996. Based on that review, the firm was informed (letter date: April 16, 1996) that DBE had no further questions, and it was emphasized that the comments expressed in that letter were preliminary, which may be revised upon complete review of the application.

Though DBE completed its review previously, the "Office-Level" approval sheet was not prepared at that time. The present reviewer was requested to prepare that sheet. In preparation for the "Office-Level" sign off, the reviewer evaluated this application in view of the following requirements for granting a waiver of in vivo bioequivalence study requirements for nasal solution sprays:

- A. Q1 and Q2 sameness of the generic and innovator formulations
- B. Device comparability
- C. The comparative performance of the drug delivery devices of the test and reference products based on the following in vitro tests:
 - 1. Unit Dose/Content Uniformity
 - 2. Priming, loss of prime, and tail off
 - 3. Droplet size distribution
 - 4. Spray pattern
 - 5. Plume geometry

The formulation of the test product is Q1 and Q2 same as that of the reference product. However, the reviewer's evaluation revealed deficiencies in data to support equivalent

in vitro performance of delivery devices of these products. Therefore, the April 6, 1996 DBE recommendation of waiver of in vivo bioequivalence study requirements should be revised. At this time the test product is not eligible for the waiver due to the following deficiencies in vitro testing.

1. ***Unit Dose/Content Uniformity:*** The unit dose data were based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from single lots¹ of the test and reference products.
2. ***Priming, loss of prime, and tail off:*** The firm should submit data (based on a validated chromatographic/chemical assay) to support comparative performance of the test and reference products with regard to priming, loss of prime, and tail off.

The reference listed drug's package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. ***Droplet Size Distribution:*** The firm determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sector (Beginning, Middle and End) sectors. The firm should perform this test using 10 units of the test and reference products.

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, the firm should submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with

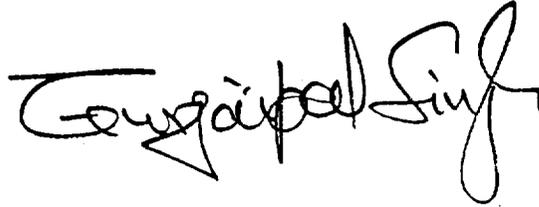
¹ This application was submitted in December 1995. At that time DBE required in vitro comparisons based on only one lot of the test reference products. Therefore, the requested tests do not need three lots of these products recommended in the June 1999 draft Nasal BA/BE guidance.

legible dimension of the pump and the actuator (including the tip, orifice, and actuator insert nominal spray angle).

Recommendation

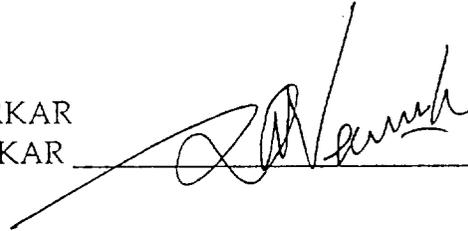
The in vitro testing conducted by Barre-National (ALPHARMA) comparing its cromolyn sodium nasals sprays (5.2 mg/spray, 26- and 13-mL sizes) and the reference product (Nasalcrom® · Pharmacia and Upjohn, 5.2 mg/spray) is incomplete due to deficiencies 1-3.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

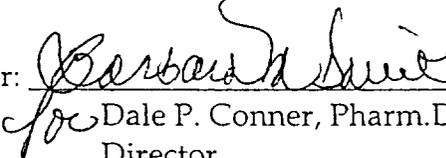


11-3-00

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR



Date 11/7/2000

Concur:  Date 11/21/00
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

September 26, 2000

MINOR AMENDMENT TO A PENDING FILE

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Gary Buehler, Acting Director

ORIG AMENDMENT
NIAM

Re: **Cromolyn Sodium Nasal Solution, USP**
ANDA #74-800

Dear Mr. Buehler:

Alpharma USPD Inc. submits a Minor Amendment to a pending application as outlined in the Agency letter of December 28, 1999.

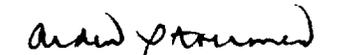
Specifically, Alpharma certifies that our nasal facility has been found to be in compliance with cGMP and has been cleared for approval of the drug product by the Baltimore District Office.

For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs.

Sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs

Sincerely,
ALPHARMA USPD INC


Arden Stoermer
Vice-President, Quality Affairs



May 30, 2000

**MINOR AMENDMENT TO A PENDING
APPLICATION**

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Gary Buehler, Acting Director

NEW CORRESP

NC

RE: ANDA 74-800
Cromolyn Sodium Nasal Solution, 40 mg/mL

Dear Mr. Buehler:

Alpharma USPD Inc submits a minor amendment to our pending application. This amendment requests Agency approval to amend a document presented in the ANDA, "Nasal Spray Facility Description" which can be found starting on page 21 (attachment 2C) of our May 6, 1998 major amendment.

The changes required to the narrative, "Nasal Spray Facility Description" are straightforward. It was apparent to us that information contained in this 1998 document did not reflect the letter or spirit of a class 100,000 facility, we undertook to amend it. We have attached to this letter a table that reviews the changes we are proposing. It should be noted that our modifications will not affect drug product quality and there are no changes to the drug product tests or specifications already submitted to the application. As there is no change to the drug product quality or specifications, we have not included a batch with this amendment.

In terms of the filing mechanism, a minor amendment, numerous conversations were held with the Agency through our consultant. Senior members of the Chemistry Division were consulted. It was agreed that the information present hereafter may reasonably be submitted as a 'minor' amendment to a pending ANDA.

If you have questions on content of this letter, please do not hesitate to contact me at (410) 277-1742.

Yours sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs

Alpharma USPD Inc.

Research & Development Center Tel (410) 298-1000
The Johns Hopkins Bayview Center Fax (410) 277-1810
333 Cassell Drive, Suite 3500
Baltimore, MD 21224



MM
6-16

DEC 28 1999

Alpharma, U.S. Pharmaceuticals Division
Attention: Martin Levy
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated December 1, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cromolyn Sodium Nasal Solution USP, 4%(40 mg/mL), packaged in 13 mL and 26 mL containers.

Reference is also made to your amendments dated March 18, 1996, April 21, and November 5, 1999.

The application is deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging or holding of the drug substance or the drug product comply with current good manufacturing practice (CGMP) regulations.

We are aware that you have notified the Agency that you are not ready for inspection. We have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application. Until such time that you can notify the Agency that you are ready for inspection, your application cannot be approved.

Your amendment to this application submitted in response to this not approvable letter will be considered as a MINOR AMENDMENT provided that the amendment contains no significant information necessary to remedy any CGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with CGMP and have been cleared for approval of this drug product by representatives of the local FDA District Office. If it is necessary for you to significantly revise your procedures, controls or practices to correct your CGMP problems, then the amendment will be considered to represent a MAJOR amendment.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RMP 12/27/99

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



November 5, 1999

FAX AMENDMENT TO A PENDING APPLICATION

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Douglas Sporn, Director

N/FA

Re: ANDA 74-800
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a)(1), Alpharma, U.S. Pharmaceutical Division hereby submits a Fax Amendment to our pending Abbreviated New Drug Application for Cromolyn Sodium Nasal Solution USP, 40 mg/mL. Reference is made to the Agency's letter dated October 14, 1999 regarding the above referenced product application (attached).

Alpharma has responded, completely and comprehensively, to each question posed by the Agency in the order it was presented in the aforementioned letter.

For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and fax is 410-558-7262.

Sincerely,
ALPHARMA USPD INC.

A handwritten signature in black ink that reads "Martin Levy".

Martin Levy, FBIRA
Director, Regulatory Affairs

MU/m
Enclosures

April 21, 1999

MAJOR AMENDMENT TO A PENDING APPLICATION

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Doug Sporn, Director

FPL
ORIG AMENDMENT
AC

Re: ANDA 74-800
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Dear Mr. Sporn:

Alpharma, U.S. Pharmaceutical Division hereby submits a Major Amendment to our pending Abbreviated New Drug Application for Cromolyn Sodium Nasal Solution USP, 40 mg/ mL. Reference is made to the Agency's letter dated November 30, 1998 (chemistry & labeling) regarding the above referenced product application.

Alpharma has responded, completely and comprehensively, to each question posed by the Agency in the order it was presented in the aforementioned letter.

We are pleased to forward 12-month real time stability data for your review. Alpharma is requesting a 24-month expiry dating for this product.

For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and fax is 410-558-7262.

Yours sincerely,
ALPHARMA USPD INC.


Martin Levy, FBIRA
Director, Regulatory Affairs
ML/fm

RECEIVED

APR 22 1999

GENERIC DRUGS

May 6, 1998

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*Drug Labeling
5/22/98*

ORIG AMENDMENT

N/A

**Re: ANDA 74-800
Cromolyn Sodium Nasal Solution USP, 40 mg/ mL**

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a)(1), Alpharma, U.S. Pharmaceutical Division hereby submits a Major Amendment to our pending Abbreviated New Drug Application for Cromolyn Sodium Nasal Solution USP, 40 mg/ mL. Reference is made to the Administration's letters dated May 23, 1996 (chemistry & labeling) and July 11, 1997 (labeling), regarding the above referenced product application (both letters attached). The Administration's comments from the 5/23/96 letter have been restated and our responses follow:

A. Chemistry Deficiencies

1.

1.
2.
3.
4.
5.

2.

1

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

5/6/98

B. LABELING DEFICIENCIES

The product labeling has been revised as requested in the Administration's 7/11/97 comment letter. Enclosed are 12 printer's proofs of the container, carton and insert labeling. Also included is a side-by-side comparison of the proposed labeling with the previously submitted labeling with the differences annotated (attachment 8).

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

- 1. Approval of the Process Validation Protocol and other SOP's for the exhibit batch(es) and scale-up batches, and audit of the data fall within the purview of FDA field investigators, and will not be part of this review.**

Alpharma acknowledges the Administration's comment regarding the responsibilities of the FDA field investigators as it relates to the approval of

the Process Validation Protocol, SOP's and data for the exhibit batch and scale-up batches.

2. The HPLC method for the active ingredient and related compounds in the drug product will be regarded as alternate to the USP methods for regulatory purposes.

Alpharma acknowledges the Administration's comment regarding the HPLC method for the active ingredient and related compounds in the drug product and their classification as alternate to the USP methods for regulatory purposes.

3. Compliance of all facilities involved in the manufacture and testing of the drug product with the current good manufacturing practice regulations will be evaluated by our Office of Compliance. A satisfactory evaluation is required prior to the approval of this application.

Alpharma acknowledges the Administration's comment regarding the cGMP compliance of all facilities involved in the manufacturing and testing of the drug product prior to the approval of this application.

4. The waiver of the *in vivo* bioequivalence study requirements and the "In-vitro Performance Evaluation of Cromolyn Sodium Nasal Solution Relative to that of the Reference Listed Drug Nasalcrom® Nasal Solution (Fisons)" have been referred to the Division of Bioequivalence for review. The result of the review may be addressed in a separate communication.

Alpharma acknowledges the Administration's comment regarding the waiver of the *in vivo* bioequivalence and the Division of Bioequivalence.

In addition to the above information the following documents are also included for review based on the revised formulation and change of the finished drug product from Rx to OTC status.

1. Patent Certification and Exclusivity Statement (attachment 9).
2. Quantitative and Qualitative Compositions (attachment 10).
3. Manufacturing and Processing Instructions, Summary of In-Process Controls, Comparative Manufacturing Summary and the blank proposed Master Product and Control Record (attachment 11).

Alpharma USPD
Cromolyn Sodium Nasal
Solution USP, 40 mg/mL
ANDA #74-800/Major Amendment

4. Executed Batch Record for lot #PN7828 (attachment 12) and Certificates of Analyses (attachment 13).
5. Manufacturer's and Alpharma's Certificates of Analysis for the active drug substance and excipients (attachment 14).
6. Container/closure release test results (attachment 15).
7. Preservative Effectiveness Test summary (attachment 16).

The following specifications have been updated and are enclosed:
Packaging Components: XCP104, XFT38 and XFT39
Raw Materials: Purified Water USP, cromolyn sodium USP

In accordance with 21 CFR § 314.96(b), Alpharma certifies that the field copy is a true copy of the major amendment to the application and has been sent to the FDA Baltimore district office.

We trust that our response fully addresses the Administration's concerns.

Sincerely,
ALPHARMA


Ronald Bynum
Manager, Regulatory Affairs
RB/fm



In accordance with 21 CFR §314.96 (b), the undersigned official certifies that Alharma, U.S. Pharmaceuticals Division has provided a field copy of this major amendment to a pending application to the FDA Baltimore district.

Ronald Bynum 5/5/98

Ronald Bynum
Manager, Regulatory Affairs

3/14/96

RRE-NATIONAL INC.

ch 13, 1996

ce of Generic Drugs,
ision of Bioequivalence, HFD-630
ention: Keith Chen, Ph.D.
ER, Food and Drug Administration
tro Park North II
OO Standish Place, Room 150
ckville, Maryland 20855-2773

NEW CORRES

BIOAVAILABILITY

NC/B10

*Note
NPI
8/26/96
4/26/96*

RECEIVED

MAR 14 1996

ANDA 74-800

Cromolyn Sodium Nasal Solution USP, 40 mg/mL

GENERIC DRUGS

Response to Telephone Request

Dear Dr. Chen:

Reference is made to the March 12, 1996 telecommunication between the Administration (Mr. Moo Park) and Barre-National Inc. (Ron Bynum) in which Mr. Park requested that Barre-National supply the report entitled: "Review, In Vitro Profiles and Performance Characteristics of Cromolyn Sodium Nasal Solution, USP (40 mg/mL)", contained on pages 49-98 of the 12/1/95 ANDA submission on an IBM compatible disk in WordPerfect 6.0 format.

Please find enclosed the requested information on an IBM compatible disk.

Sincerely,

BARRE-NATIONAL INC.



Deborah Miran
Sr. Director, Regulatory Affairs

Enclosure

f:\...\0075\submiss\bio

*Miran
4-26-96
NPI
disk*

333 Cassell Drive, Suite 3500 • Baltimore, MD 21224 • 410-558-7250

Manufacturing Facilities: 7205 Windsor Blvd • Baltimore, MD 21244 • 410-298-1000
P.O. Box 898 • Riverview Rd • Lincolnton, NC 28093 • 704-735-5700

1-1
BARRE-NATIONAL INC.

March 18, 1996

PROAVAILABILITY

Office of Generic Drugs,
Attention: Mark Anderson, CSO
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

3/22/96
RECEIVED
NC/Bio
Noted HAT
jmuft
4/4/96

RECEIVED

MAR 20 1996

GENERIC DRUGS

Re: **ANDA 74-800**
Cromolyn Sodium Nasal Solution USP, 40 mg/mL

Response to Telephone Request

Dear Mr. Anderson:

Reference is made to the March 15, 1996 telecommunication between yourself and Barre-National Inc. (Ron Bynum) in which you informed us that the IBM compatible disk supplied to Mr. Moo Park of the Division of Bioequivalence on March 13, 1996 contained a virus.

Barre-National apologizes to the Administration for the previously submitted disk containing the virus.

Please find enclosed a replacement disk which has been checked using Norton Anti-Virus and found to be virus free. As requested the report entitled: "Review, In Vitro Profiles and Performance Characteristics of Cromolyn Sodium Nasal Solution, USP (40 mg/mL)", contained on pages 49-98 of the 12/1/95 ANDA submission is included on the enclosed IBM compatible disk in WordPerfect 6.0 format.

Sincerely,

BARRE-NATIONAL INC.

Vincent Addino
for

Deborah Miran
Sr. Director, Regulatory Affairs

Enclosure

f:\...10075\submiss\bio

333 Cassell Drive, Suite 3500 • Baltimore, MD 21224 • 410-558-7250

Manufacturing Facilities: 7205 Windsor Blvd • Baltimore, MD 21244 • 410-298-1000
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10-24
C. B. B. B.

Barre-National, Inc
Attention: Deborah Miran
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

MAY 23 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 1, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cromolyn Sodium Nasal Solution USP, 40 mg/mL, 5.2 mg/Inhalation.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

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B. LABELING DEFICIENCIES

1. GENERAL COMMENT

On all labels and labeling, we prefer the expression of strength be expressed prominently and in conjunction the established name as:

4 %

2. CONTAINER (13 mL and 26 mL)

a. Front Panel

i. Please assure the total net quantity does not appear in conjunction with the established name and strength.

ii. Add the following statement:

Each actuation unit delivers a metered spray containing 5.2 mg of Cromolyn.

- b. Right Panel, Note - Insert "Usual Dosage" prior to "See package insert..."
- 3. CARTON (1 x 13 mL and 1 x 26 mL)

See comments under CONTAINER.

4. INSERT

I. PHYSICIAN

a. DESCRIPTION

- i. Revise to read "molecular formula" rather than "empirical formula".
- ii. Replace "molecular structure" with "structural formula".
- iii. Include the molecular weight.

b. INDICATIONS

Revise this section heading to read:

INDICATIONS AND USAGE

c. PRECAUTIONS

- i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Delete "and" from this section heading.
- ii. Pregnancy - Revise this subsection heading to read as follows:

Pregnancy: Teratogenic Effects,
Pregnancy Category B.

II. PATIENT INSTRUCTION SHEET - Satisfactory.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Approval of the Process Validation Protocol and other SOP's for the exhibit batch(es) and scale-up batches, and audit of the data fall within the purview of FDA field investigators, and will not be part of this review.
2. The method for the active ingredient and related compounds in the drug product will be regarded as alternate to the USP methods for regulatory purposes.
3. Compliance of all facilities involved in the manufacture and testing of the drug product with the current good manufacturing practice regulations will be evaluated by our Office of Compliance. A satisfactory evaluation is required prior to the approval of this application.
4. The waiver of the *in vivo* bioequivalence study requirements and the "In-vitro Performance Evaluation of Cromolyn Sodium Nasal Solution Relative to that of the Reference Listed Drug Nasalcrom[®] Nasal Solution (Fisons)" have been referred to the Division of Bioequivalence for review. The result of the review may be addressed in a separate communication.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

 5/11/91

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

ANDA 74-800

Barre-National
Attention: Deborah Winkel
John Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore MD 21224

APR 16 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 40 mg/mL, 13 mL and 26 mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,



Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-800

Barre-National, Inc.
Attention: Deborah Miran
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

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.

NAME OF DRUG: Cromolyn Sodium Nasal Solution USP, 40 mg/mL;
5.2 mg/Inhalation

DATE OF APPLICATION: December 1, 1995

DATE OF RECEIPT: December 4, 1995

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.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Consumer Safety Officer
(301) 594-0370

Sincerely yours,
Jerry Phillips 2/2/96
Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-800
cc:

Endorsement:

1 1/20/96

BARRE-NATIONAL INC.

December 1, 1995

Charles Ganley M.D., Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*505 (j)(2)(A) info for
acceptable for filing
12/1/95
9/6/95*

Re: **Abbreviated New Drug Application**
Cromolyn Sodium Nasal Solution, 40 mg/mL

*labeling
forms
completed
8-13-94*

Dear Dr. Ganley:

We are herewith submitting an Abbreviated New Drug Application pursuant to 21 CFR §314.94(a) and Section 505(j) of the Federal Food, Drug and Cosmetic Act for the drug product Cromolyn Sodium Nasal Solution, 40 mg/mL.

The abbreviated application is being submitted as follows:

- 1) **Archival Copy** (Blue Folder) - consisting of one volume which contains items required for an ANDA per 21 CFR section 314.94(a) plus all the information required under section 505(j)(2)(A)(B) of the FD&C Act (see Table of Contents of this application). Under separate cover, as required by the final rule dated September 8, 1993, Barre-National Inc. hereby certifies that a field copy that contains (a) the technical section required by 21 CFR §314.94(a)(9), (b) a copy of the 356h form, and (c) a certification that the copy of the technical section is the same as that contained in the archival and review copies has been sent simultaneously to the Baltimore District Office.
- 2) **Review Copy** - which contains items for an ANDA per 21 CFR 314.94(d)(2) in two separate sections:

Red Folder - Items described under 314.94(a)(2) through (a)(6), (a)(8), (a)(9), analytical methods, and analytical methods validation.

Orange Folder - Items described under 314.94(a)(3), (a)(7), and (a)(8).

Sincerely,

BARRE-NATIONAL INC.

*Vincent Andolina
for*

Deborah Miran
Senior Director, Regulatory Affairs

RECEIVED

DEC 04 1995

GENERIC DRUGS

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BARRE-NATIONAL INC.

December 1, 1995

Mr. Gary Pierce
Acting District Director
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

Re: **Abbreviated New Drug Application**
Cromolyn Sodium Nasal Solution, 40 mg/mL

Dear Mr. Pierce:

Pursuant to 21 CFR § 314.94 (d) (5), Barre-National of Baltimore, Maryland hereby submits a field copy of our abbreviated new drug application, Cromolyn Sodium Nasal Solution, 40 mg/mL.

The undersigned official certifies that Barre-National's field copy is a true copy of that submitted to the Food and Drug Administration's headquarters.

Sincerely,
BARRE-NATIONAL INC.

Vincent Andolina
for

Deborah Miran
Senior Director, Regulatory Affairs

Enclosures
DM:fm

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