DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-102 **NDA APPROVAL**

Fleming & Company, Pharmaceuticals
Attention: Phillip W. Dritsas, President
1733 Gilsinn Lane
Fenton, MO 63026

Dear Mr. Dritsas:

Please refer to your new drug application (NDA) dated September 26, 2006, received September 27, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CaloMist (cyanocobalamin, USP) Nasal Spray, 25 mcg/0.1 mL.

We acknowledge receipt of your submissions dated January 22, February 16, March 15, June 21, July 3 and 27, 2007.

This new drug application provides for the use of CaloMist (cyanocobalamin, USP) Nasal Spray for maintenance of vitamin B12 concentrations after normalization with intramuscular vitamin B12 therapy in patients with vitamin B12 deficiency who have no nervous system involvement.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and with the minor editorial revisions listed below, as discussed in a telephone conversation between Christina Patullo and George Love of Fleming & Company, Pharmaceuticals, and Jennifer Johnson and Lina AlJuburi of this Division on July 27, 2007.

1. This revision applies only to the carton label. Please insert the statement **"NOTE: See patient instruction sheet for important information about priming the nasal spray bottle"** in the Patient Dosing Instructions listed on the carton label. This statement should replace the current statement which reads,

2. This revision applies to all labeling (carton, container, package insert, patient instruction sheet). Currently, the established name "cyanocobalamin, USP" does not state the final dosage form (nasal spray). Please indicate the final dosage form with the established name. "CaloMist Nasal Spray (cyanocobalamin, USP)" should be changed to "CaloMist (cyanocobalamin, USP) Nasal Spray". Throughout the package insert and patient instruction sheet, please change "CaloMist Nasal Spray" to "CaloMist".

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to, except for including the revisions listed above, the enclosed labeling (text for package insert and text for patient package insert). These revisions are terms of the NDA approval. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA 22-102."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels (submitted on July 27, 2007), except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-102**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package inserts to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form.

For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert, Patient Instruction Sheet, Immediate Carton Labels and Container Labels

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Calo*Mist*™ Nasal Spray safely and effectively. See full prescribing information for Calo*Mist* Nasal Spray.

Calo*Mist* Nasal Spray (cyanocobalamin, USP)
Initial U.S. Approval: 1942

----------INDICATIONS AND USAGE----------
Calo*Mist* Nasal Spray is a vitamin B_{12} indicated for:
- Maintenance of vitamin B_{12} concentrations after normalization with intramuscular vitamin B_{12} therapy in patients with vitamin B_{12} deficiency who have no nervous system involvement (1.1)

Important Limitations of Use: Calo*Mist* Nasal Spray has not been evaluated for the treatment of newly diagnosed vitamin B_{12} deficiency (1.2).

----------DOSAGE AND ADMINISTRATION----------
- One spray in each nostril daily (25 mcg per nostril, total daily dose 50 mcg) (2.1)
- One spray in each nostril twice daily for patients with an inadequate response to once daily dosing (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Nasal spray: 25 mcg cyanocobalamin, USP /0.1 mL (3)

----------CONTRAINDICATIONS----------
- Sensitivity to cobalt, vitamin B_{12}, or any component of this product (4)

----------WARNINGS AND PRECAUTIONS----------
- Vitamin B_{12} concentrations must be monitored. Patients with declining or abnormally low vitamin B_{12} concentrations should be switched back to intramuscular vitamin B_{12} injections (5.1)
- Effectiveness in patients with nasal pathology or with other concomitant intranasal drugs has not been determined. Use with caution (5.2)
- Cyanocobalamin causes optic nerve atrophy in patients with Leber's disease. Do not use (5.3)
- Anaphylaxis and angioedema have been reported with parenteral vitamin B_{12} products (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (> 4%) were rhinorrhea, nasopharyngitis, arthralgia, dizziness, headache, nasal discomfort, pain, bronchitis, and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fleming Pharmaceuticals at 1-800-343-0164 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Patients with vitamin B_{12} deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B_{12} therapy (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Vitamin B_{12} Deficiency

Calo*Mist* Nasal Spray is indicated for maintenance of vitamin B_{12} concentrations after normalization with intramuscular vitamin B_{12} therapy in patients with vitamin B_{12} deficiency who have no nervous system involvement.

1.2 Important Limitations of Use

Calo*Mist* Nasal Spray has not been evaluated for the treatment of newly diagnosed vitamin B_{12} deficiency.

Calo*Mist* Nasal Spray is not suitable for use in the vitamin B_{12} absorption test (Schilling Test).

The effectiveness of Calo*Mist* Nasal Spray in patients with nasal pathology (e.g., nasal congestion, allergic rhinitis, upper respiratory infections) has not been determined. Treatment with Calo*Mist* Nasal Spray should be deferred until nasal symptoms have subsided [*see Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended initial dose of Calo*Mist* Nasal Spray is one spray in each nostril once daily (25 mcg per nostril, total daily dose 50 mcg). The dose should be increased to one spray in each nostril twice daily (total daily dose 100 mcg) for patients with an inadequate response to once daily dosing.

The dosing of Calo*Mist* Nasal Spray and other intranasal medications should be separated by several hours, and these patients should have more frequent monitoring of vitamin B_{12} concentrations because of the potential for erratic absorption.

2.2 Priming (Activation) of Pump

The pump must be primed before the bottle is used for the first time. To prime the pump, place the nozzle between the first and second finger with the thumb on the bottom of the bottle. Pump the unit firmly and quickly then repeat this priming an additional 6 times for a total of 7 priming sprays. Now the nasal spray is ready for first-time use. If 5 or more days elapse since last use, the pump must be re-primed with two re-priming sprays.

Additional instructions are provided in the patient instruction sheet [*see Patient Counseling Information (17.2)*].

3 DOSAGE FORMS AND STRENGTHS

Calo*Mist* Nasal Spray (cyanocobalamin, USP) is a solution of cyanocobalamin, USP, for administration as a metered spray to the nasal mucosa. Each bottle of Calo*Mist* Nasal Spray contains 18 mL of a 25 mcg/0.1 mL solution of cyanocobalamin. The spray solution has a pH between 6.5 and 7.5. After initial priming, each spray delivers 25 mcg of cyanocobalamin. Each bottle will deliver 60 sprays for a total of thirty 50 mcg doses of Calo*Mist* Nasal Spray.

4 CONTRAINDICATIONS

Sensitivity to cobalt, vitamin B_{12}, or any component of this product [*see Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Laboratory Monitoring

Hematocrit, reticulocyte count, vitamin B_{12}, folate, and iron levels should be obtained prior to treatment. All hematologic parameters, including vitamin B_{12} concentrations, should be normal before initiating treatment with Calo*Mist* Nasal Spray. Periodic monitoring of serum vitamin B_{12} concentrations must be obtained to confirm adequacy of therapy. Vitamin B_{12} concentrations and complete blood counts should be monitored one month after starting Calo*Mist* Nasal Spray and then at 3 to 6 month intervals thereafter. Patients with borderline-low vitamin B_{12} concentrations (<300 ng/L) should also undergo measurement of methylmalonic acid and homocysteine concentrations, which are more sensitive measures of vitamin B_{12} deficiency in this setting.

Patients with declining or abnormally low vitamin B_{12} concentrations despite maximal doses of Calo*Mist* Nasal Spray should be switched back to intramuscular vitamin B_{12} injections. Vitamin B_{12} deficiency that is inadequately treated for longer than three months may produce irreversible neurological damage.

5.2 Use in Patients With Nasal Pathology

Calo*Mist* Nasal Spray has not been evaluated in patients with nasal pathology. Treatment with Calo*Mist* Nasal Spray should be deferred until nasal symptoms have subsided. Patients with chronic nasal symptoms or significant nasal pathology are not ideal candidates for intranasal vitamin B_{12} therapy. If Calo*Mist* Nasal Spray therapy is attempted in these patients, vitamin B_{12} concentrations should be monitored more frequently than in patients without nasal pathology because of the potential for erratic or blunted absorption.

5.3 Use in Patients with Leber's Disease

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with cyanocobalamin suffered severe and swift optic atrophy. Cyanocobalamin should not be used in these patients.

5.4 Anaphylaxis and Angioedema

Anaphylactic shock, death, and angioedema were not reported in the Calo*Mist* Nasal Spray clinical trial but have been reported with parenteral vitamin B_{12} administration.

5.5 Megaloblastic Anemia

Megaloblastic anemia has many causes, including vitamin B_{12} deficiency and folate deficiency. Folic acid may result in a hematological response in patients with vitamin B_{12} deficiency, but will not prevent irreversible neurological manifestations. Vitamin B_{12} is not an appropriate treatment for folate deficiency.

Hypokalemia, thrombocytosis, and sudden death may occur when severe megaloblastic anemia is treated intensely with vitamin B_{12}. Serum potassium and the platelet count should be carefully monitored in this setting.

5.6 Blunted Response to Vitamin B_{12} Therapy

Infections, uremia, concurrent iron or folic acid deficiency, and drugs with bone marrow suppressant properties (e.g., chloramphenicol) may blunt the therapeutic response to vitamin B_{12} products, including Calo*Mist* Nasal Spray.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below and in Table 1 reflect exposure in 25 subjects (age range 27-82 years; 17 women; 21 Caucasians) with vitamin B_{12} deficiency (12 with pernicious anemia, 4 secondary to gastrointestinal surgery, 9 with unknown cause) who received Calo*Mist* Nasal Spray 50 mcg daily for 8 weeks in an uncontrolled clinical trial. Prior to enrollment, all subjects were required to have normal vitamin B_{12} levels with intramuscular vitamin B_{12} injections. One patient who completed the study developed epistaxis on Day 12 of dosing and was noted to have irritation of the right nasal septum at study end. This patient had pre-existing allergic rhinitis and required a doubling of the Calo*Mist* Nasal Spray dose during the last week of the study because of declining vitamin B_{12} concentrations.

Table 1. Potentially related adverse reactions reported during 8 weeks of treatment with Calo*Mist* Nasal Spray in an uncontrolled clinical trial.

Preferred Term	Calo*Mist* Nasal Spray (N=25) n (%)
Arthralgia	3 (12%)
Dizziness	3 (12%)
Headache	3 (12%)
Nasopharyngitis	3 (12%)
Rhinorrhea	3 (12%)
Bronchitis	2 (8%)
Nasal Discomfort	2 (8%)
Pain	2 (8%)
Rash	2 (8%)
Asthma	1 (4%)
Back Pain	1 (4%)
Cough	1 (4%)
Epistaxis	1 (4%)
Hypersomnia	1 (4%)
Influenza Like Illness	1 (4%)
Malaise	1 (4%)
Pharyngolaryngeal Pain	1 (4%)
Postnasal Drip	1 (4%)
Procedural Pain	1 (4%)
Pyrexia	1 (4%)
Scab	1 (4%)

Sinus Headache	1 (4%)
Sinusitis	1 (4%)
Tooth Abscess	1 (4%)

6.2 Experience with Parenteral Vitamin B_{12}

The following adverse reactions have been reported with parenteral vitamin B_{12}:

Generalized:	Anaphylactic shock and death
Cardiovascular:	Pulmonary edema and congestive heart failure early in treatment
	Peripheral vascular thrombosis
Hematological	Polycythemia vera
Gastrointestinal:	Mild transient diarrhea
Dermatological:	Itching; transitory exanthema

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of cyanocobalamin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Angioedema and angioedema-like reactions *[See Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS

Most antibiotics, methotrexate, and pyrimethamine invalidate the vitamin B_{12} diagnostic blood assays.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with Calo*Mist* Nasal Spray. Although vitamin B_{12} is an essential vitamin and requirements are increased during pregnancy, it is not known whether Calo*Mist* Nasal Spray can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Calo*Mist* Nasal Spray should be given to a pregnant woman only if clearly needed. Adequate and well-controlled studies have not been conducted in pregnant women.

8.3 Nursing Mothers

Although vitamin B_{12} is an essential vitamin and requirements are increased during lactation, it is not known whether Calo*Mist* Nasal Spray can cause harm to an infant when administered to a nursing woman. Vitamin B_{12} appears in the milk of nursing mothers in concentrations that approximate the mother's vitamin B_{12} blood level. Caution should be exercised when Calo*Mist* Nasal Spray is administered to a nursing woman.

8.4 Pediatric Use

Because Calo*Mist* Nasal Spray has not been studied in children, safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

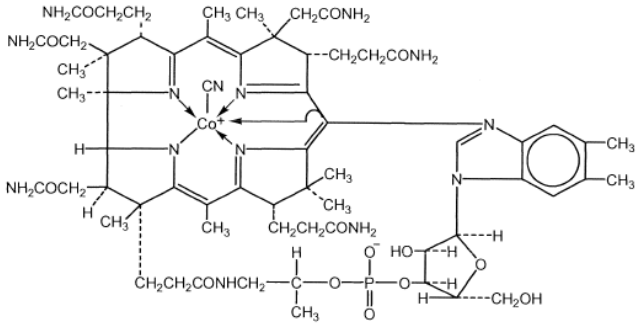
Clinical studies of Calo*Mist* Nasal Spray did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal/Hepatic Impairment

Patients with vitamin B_{12} deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B_{12} therapy.

11 DESCRIPTION

Cyanocobalamin is a synthetic form of vitamin B_{12} with activity equivalent to the endogenous form of vitamin B_{12}. The chemical name is α-(5,6-dimethylbenzimidazolyl) cyanocobamide. The cobalt content is 4.35%. The molecular formula is $C_{63}H_{88}CoN_{14}O_{14}P$, which corresponds to a molecular weight of 1355.4 and the following structural formula:



Cyanocobalamin occurs as dark red crystals, orthorhombic needles, or crystalline red powder and is very hygroscopic in the anhydrous form, and sparingly to moderately soluble in water (1:80). The pharmacologic activity of cyanocobalamin is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (Vitamin C), but not by autoclaving for short periods of time (15-20 minutes) at 121°C. The vitamin B_{12} coenzymes are very unstable in light.

Each bottle of Calo*Mist* Nasal Spray contains cyanocobalamin, sodium chloride, sodium phosphate monobasic, benzyl alcohol, sodium hydroxide, and benzalkonium chloride in purified water with an attached spray pump unit.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

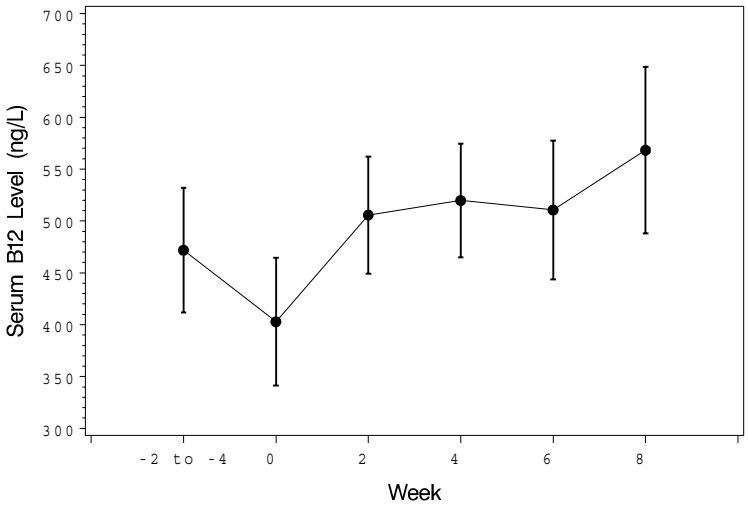
Vitamin B_{12} is essential for growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Rapidly dividing cells (e.g., epithelial cells, bone marrow, myeloid cells) have the greatest requirement for vitamin B_{12}. In tissues, vitamin B_{12} is essential for the conversion of methylmalonate to succinate and for the synthesis of methionine from homocysteine. In the absence of vitamin B_{12}, tetrahydrofolate cannot be regenerated from 5-methyl tetrahydrofolate, and functional folate deficiency occurs. Vitamin B_{12} also may be involved in sulfhydryl-activated enzyme systems associated with fat and carbohydrate metabolism and protein synthesis.

12.2 Pharmacodynamics

In 24 vitamin B_{12} deficient patients who were stabilized on intramuscular (IM) vitamin B_{12} therapy, once daily intranasal dosing with Calo*Mist* Nasal Spray for 8 weeks resulted in serum vitamin B_{12} concentrations that were within the target range (>200 ng/L) and slightly higher than those seen 2 to 4 weeks after administration of IM vitamin B_{12} (see Figure 1 - average mean increase from Visit 1 to Visits 3-6 = 45 ng/L). Twenty-three of these 24 patients received 50 mcg of Calo*Mist* Nasal Spray daily for the duration of the trial; the remaining patient required doubling of the Calo*Mist* Nasal Spray dose from 50 mcg to 100 mcg daily during the last week of the study because of declining vitamin B_{12} concentrations. One of the 25 patients dosed with Calo*Mist* Nasal Spray was excluded from the efficacy analyses because a diagnosis of vitamin B_{12} deficiency could not be confirmed.

Figure 1.

Mean Vitamin B_{12} Serum Levels Over 8 Weeks of Intranasal (IN) Vitamin B_{12} Dosing in 24 Subjects Stabilized on Intramuscular (IM) Vitamin B_{12}



Notes:

- Weeks -2 to -4 correspond to 2 to 4 weeks post last IM injection
- Calo*Mist* Nasal Spray was initiated at Week 0.
- Figure shows mean vitamin B_{12} serum levels with 95% confidence intervals.

12. 3 Pharmacokinetics

Distribution

In the blood, vitamin B_{I2} is bound to transcobalamin II (a specific B-globulin carrier protein) and is distributed to tissues and stored primarily in the liver and bone marrow.

Elimination

About 3-8 mcg of vitamin B_{12} is secreted into the gastrointestinal tract daily via the bile. In subjects with sufficient intrinsic factor, all but about 1 mcg is reabsorbed. When vitamin B_{12} is administered in doses that saturate the binding capacity of plasma proteins and the liver, the unbound vitamin B_{12} is rapidly eliminated in the urine. Retention of vitamin B_{12} in the body is dose-dependent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no long-term studies in animals that have evaluated the carcinogenic potential of any of the vitamin B_{12} products, including Calo*Mist* Nasal Spray. There is no evidence from long-term use in patients with pernicious anemia that vitamin B_{12} is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this malignancy has been attributed to the underlying pathology of pernicious anemia and not to treatment with vitamin B_{12}.

16 HOW SUPPLIED/STORAGE AND HANDLING

Calo*Mist* Nasal Spray is available as a metered dose spray in 30 mL plastic bottles containing 18 mL of solution. Calo*Mist* Nasal Spray is available in a dosage strength of 25 mcg cyanocobalamin, USP, per actuation (0.1 mL/actuation). Calo*Mist* Nasal Spray is provided in a carton containing one bottle of nasal spray solution affixed with a nasal spray pump, a package insert, and a patient instruction sheet. One bottle delivers thirty 50 mcg doses (60 sprays) (NDC 0256-0203-01).

Storage

Protect from light. Store upright at a controlled temperature of 15 to 30°C (59 to 86°F).

Protect from freezing.

17 PATIENT COUNSELING INFORMATION

[*See FDA-approved Patient Labeling (17.2)***]**

17.1 Important Information for Patients

Patients with a chronic underlying cause of vitamin B_{12} deficiency will require indefinite administration of a vitamin B_{12} product, such as Calo*Mist* Nasal Spray. Noncompliance or inadequate treatment with vitamin B_{12} therapy may result in recurrence of anemia and the development or worsening of irreversible neurological damage.

The dosing of Calo*Mist* Nasal Spray and other intranasal medications should be separated by several hours.

Vitamin B_{12} concentrations should be monitored one month after Calo*Mist* Nasal Spray initiation or dose change and every 3-6 months thereafter.

Careful instructions on the priming of the actuator and nasal administration of Calo*Mist* Nasal Spray should be given to the patient, and the procedures for use should be demonstrated.

17.2 Patient Instruction Sheet

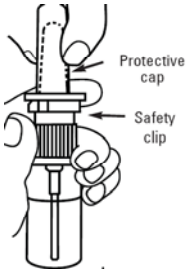
Instructions for Using Calo*Mist* Nasal Spray. Read the following instructions carefully before using Calo*Mist* Nasal Spray.

- Use **Calo*Mist*** Nasal Spray as directed by your doctor.

NOTE: Calo*Mist* Nasal Spray is prefilled to give 30 doses (60 sprays of medicine). One dose is one spray in each nostril once a day.

Calo*Mist* Nasal Spray Pump Priming: Before you use the medicine for the first time the nasal spray pump unit must be readied (primed).

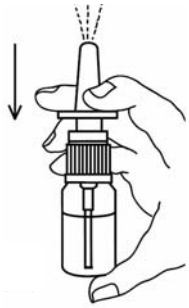
Diagram 1



1. Hold the nasal spray bottle upright with your index finger on top of one of the two arms of the pump. Remove the clear protective cap from the top of the nozzle. *(See Diagram 1)*

2. Remove the safety clip from the nasal spray pump. *(See Diagram 1)*

Diagram 2



3. While holding the nasal spray bottle upright with your index and middle fingers on the two side arms of the pump, and your thumb on the bottom of the bottle, press the arms down firmly and quickly. *(See Diagram 2)*

4. Repeat Step 3, 6 more times for a total of 7 priming sprays. You should see a full spray of medicine with the 7th priming spray. *(See Diagram 2)*

NOTE: You must prime Calo*Mist* Nasal Spray with two re-priming sprays if you do not use for five days or more.

Your Calo*Mist* Nasal Spray is now ready to use.

Diagram 3

1. Blow your nose gently to clear both nostrils. *(See Diagram 3)*

2. Hold the nasal spray bottle upright with your first and second fingers on the two side arms of the pump, and your thumb on the bottom of the bottle. *(See Diagram 4)*

3. Gently insert the nasal spray pump to one nostril (about ½ inch), pointing the tip towards the back of the nose. *(See Diagram 4)*

Diagram 4

4. With your other hand (the one not holding the bottle) use a finger to gently push close your other nostril (the one without a spray pump inserted). *(See Diagram 4)*

5. Tilt your head forward and press the arms of the nasal spray bottle down firmly and quickly.

6. Sniff in gently during and right after a spray and return your head to an upright position. Repeat these steps for the other nostril.

7. Wipe the nozzle of the nasal spray pump with a clean tissue after use. Replace the safety clip and clear cover on the nasal spray pump.

8. Store Calo*Mist* Nasal Spray upright at room temperature, 59 to 86° F (15 to 30° C). Do not freeze.

Discard Calo*Mist* Nasal Spray after 30 doses (60 sprays).

1. Unscrew the cap, rinse the bottle and pump assembly under a water faucet.
2. Dispose of all parts in a trashcan.

Keep Calo*Mist* Nasal Spray and all medicines out of the reach of children.

Manufactured by:
Fleming Pharmaceuticals
Fenton, MO 63026 USA
calomist@flemingcompany.com
1-800-343-0164

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/s/

Theresa Kehoe
7/27/2007 10:28:30 PM
Theresa Kehoe for Mary Parks