

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALOMIST safely and effectively. See full prescribing information for CALOMIST.

CALOMIST (cyanocobalamin, usp) spray, metered for nasal use
Initial U.S. Approval: 1942

RECENT MAJOR CHANGES

Dosage Forms and Strengths (3) 6/2008

INDICATIONS AND USAGE

CaloMist is a vitamin B₁₂ indicated 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 (1.1)

Important Limitations of Use: CaloMist has not been evaluated for the treatment of newly diagnosed vitamin B₁₂ 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 B₁₂, or any component of this product (4)

WARNINGS AND PRECAUTIONS

- Vitamin B₁₂ concentrations must be monitored. Patients with declining or abnormally low vitamin B₁₂ concentrations should be switched back to intramuscular vitamin B₁₂ 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 B₁₂ 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 tel:1-800-343-0164 and or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Patients with vitamin B₁₂ deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B₁₂ therapy (8.6)

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

Revised: 03/2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Vitamin B₁₂ Maintenance Therapy

CaloMist is indicated 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.

1.2 Important Limitations of Use

CaloMist has not been evaluated for the treatment of newly diagnosed vitamin B₁₂ deficiency.

CaloMist is not suitable for use in the vitamin B₁₂ absorption test (Schilling Test).

The effectiveness of CaloMist in patients with nasal pathology (e.g., nasal congestion, allergic rhinitis, upper respiratory infections) has not been determined. Treatment with CaloMist 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 CaloMist 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 CaloMist and other intranasal medications should be separated by several hours, and these patients should have more frequent monitoring of vitamin B₁₂ 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

CaloMist (cyanocobalamin, USP) Nasal Spray is a solution of cyanocobalamin, USP, for administration as a metered spray to the nasal mucosa. Each bottle of CaloMist contains 10.7 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 CaloMist.

4 CONTRAINDICATIONS

Sensitivity to cobalt, vitamin B₁₂, or any component of this product [*see Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Laboratory Monitoring

Hematocrit, reticulocyte count, vitamin B₁₂, folate, and iron levels should be obtained prior to treatment. All hematologic parameters, including vitamin B₁₂ concentrations, should be normal before initiating treatment with CaloMist. Periodic monitoring of serum vitamin B₁₂ concentrations must be obtained to confirm adequacy of therapy. Vitamin B₁₂ concentrations and complete blood counts should be monitored one month after starting CaloMist and then at 3 to 6 month intervals thereafter. Patients with borderline-low vitamin B₁₂ concentrations (<300 ng/L) should also undergo measurement of methylmalonic acid and homocysteine concentrations, which are more sensitive measures of vitamin B₁₂ deficiency in this setting.

Patients with declining or abnormally low vitamin B₁₂ concentrations despite maximal doses of CaloMist should be switched back to intramuscular vitamin B₁₂ injections. Vitamin B₁₂ deficiency that is inadequately treated for longer than three months may produce irreversible neurological damage.

5.2 Use in Patients With Nasal Pathology

CaloMist has not been evaluated in patients with nasal pathology. Treatment with CaloMist should be deferred until nasal symptoms have subsided. Patients with chronic nasal symptoms or significant nasal pathology are not ideal candidates for intranasal vitamin B₁₂ therapy. If CaloMist therapy is attempted in these patients, vitamin B₁₂ 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 CaloMist clinical trial but have been reported with parenteral vitamin B₁₂ administration.

5.5 Megaloblastic Anemia

Megaloblastic anemia has many causes, including vitamin B₁₂ deficiency and folate deficiency. Folic acid may result in a hematological response in patients with vitamin B₁₂ deficiency, but will not prevent irreversible neurological manifestations. Vitamin B₁₂ is not an appropriate treatment for folate deficiency.

Hypokalemia, thrombocytosis, and sudden death may occur when severe megaloblastic anemia is treated intensely with vitamin B₁₂. Serum potassium and the platelet count should be carefully monitored in this setting.

5.6 Blunted Response to Vitamin B₁₂ 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 B₁₂ products, including CaloMist.

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 B₁₂ deficiency (12 with pernicious anemia, 4 secondary to gastrointestinal surgery, 9 with unknown cause) who received CaloMist 50 mcg daily for 8 weeks in an uncontrolled clinical trial. Prior to enrollment, all subjects were required to have normal vitamin B₁₂ levels with intramuscular vitamin B₁₂ 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 CaloMist dose during the last week of the study because of declining vitamin B₁₂ concentrations.

Table 1. Potentially related adverse reactions reported during 8 weeks of treatment with CaloMist in an uncontrolled clinical trial.

Preferred Term	CaloMist(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 B₁₂

The following adverse reactions have been reported with parenteral vitamin B₁₂:

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 B₁₂ diagnostic blood assays.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with CaloMist. Although vitamin B₁₂ is an essential vitamin and requirements are increased during pregnancy, it is not known whether CaloMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CaloMist 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 B₁₂ is an essential vitamin and requirements are increased during lactation, it is not known whether CaloMist can cause harm to an infant when administered to a nursing woman. Vitamin B₁₂ appears in the milk of nursing mothers in concentrations that approximate the mother's vitamin B₁₂ blood level. Caution should be exercised when CaloMist is administered to a nursing woman.

8.4 Pediatric Use

Because CaloMist has not been studied in children, safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

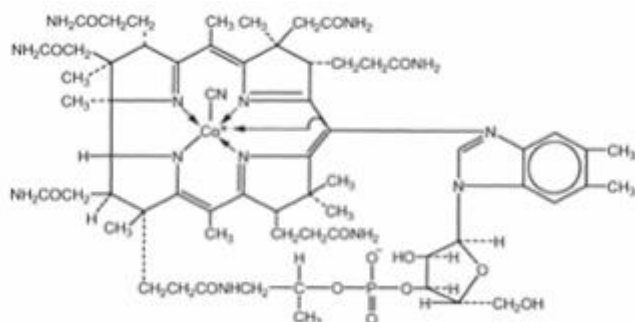
Clinical studies of CaloMist did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection 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 B₁₂ deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B₁₂ therapy.

11 DESCRIPTION

Cyanocobalamin is a synthetic form of vitamin B₁₂ with activity equivalent to the endogenous form of vitamin B₁₂. The chemical name is α -(5,6-dimethylbenzimidazolyl) cyanocobamide. The cobalt content is 4.35%. The molecular formula is C₆₃H₈₈CoN₁₄O₁₄P, 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 B₁₂ coenzymes are very unstable in light.

Each bottle of CaloMist 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

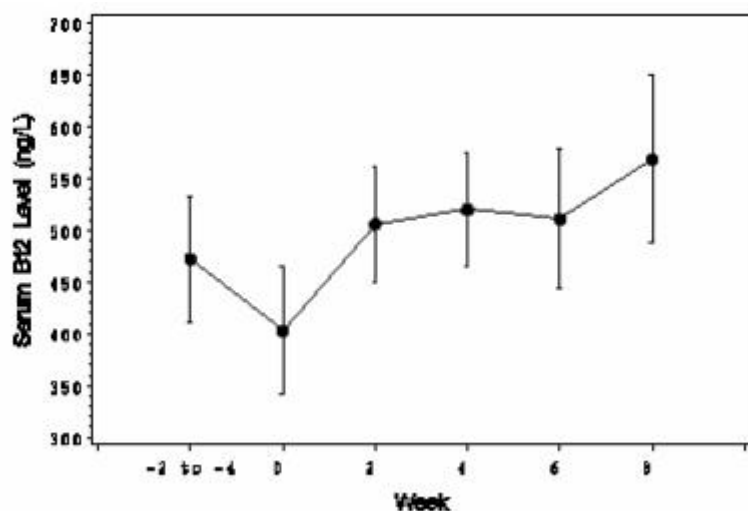
12.1 Mechanism of Action

Vitamin B₁₂ 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 B₁₂. In tissues, vitamin B₁₂ is essential for the conversion of methylmalonate to succinate and for the synthesis of methionine from homocysteine. In the absence of vitamin B₁₂, tetrahydrofolate cannot be regenerated from 5-methyl tetrahydrofolate, and functional folate deficiency occurs. Vitamin B₁₂ also may be involved in sulfhydryl-activated enzyme systems associated with fat and carbohydrate metabolism and protein synthesis.

12.2 Pharmacodynamics

In 24 vitamin B₁₂ deficient patients who were stabilized on intramuscular (IM) vitamin B₁₂ therapy, once daily intranasal dosing with CaloMist for 8 weeks resulted in serum vitamin B₁₂ 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 B₁₂ (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 CaloMist daily for the duration of the trial; the remaining patient required doubling of the CaloMist dose from 50 mcg to 100 mcg daily during the last week of the study because of declining vitamin B₁₂ concentrations. One of the 25 patients dosed with CaloMist was excluded from the efficacy analyses because a diagnosis of vitamin B₁₂ deficiency could not be confirmed.

Figure 1. Mean Vitamin B₁₂ Serum Levels Over 8 Weeks of Intranasal (IN) Vitamin B₁₂ Dosing in 24 Subjects Stabilized on Intramuscular (IM) Vitamin B₁₂



Notes:

- Weeks -2 to -4 correspond to 2 to 4 weeks post last IM injection
- CaloMist was initiated at Week 0

- Figure shows mean vitamin B₁₂ serum levels with 95% confidence intervals.

12.3 Pharmacokinetics

Distribution

In the blood, vitamin B₁₂ 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 B₁₂ 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 B₁₂ is administered in doses that saturate the binding capacity of plasma proteins and the liver, the unbound vitamin B₁₂ is rapidly eliminated in the urine. Retention of vitamin B₁₂ in the body is dose-dependent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment Of Fertility

There are no long-term studies in animals that have evaluated the carcinogenic potential of any of the vitamin B₁₂ products, including CaloMist. There is no evidence from long-term use in patients with pernicious anemia that vitamin B₁₂ 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 B₁₂.

16 HOW SUPPLIED/STORAGE AND HANDLING

CaloMist is available as a metered dose spray in 30 mL plastic bottles containing 10.7 mL of solution. CaloMist is available in a dosage strength of 25 mcg cyanocobalamin, USP, per actuation (0.1 mL/actuation). CaloMist 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 B₁₂ deficiency will require indefinite administration of a vitamin B₁₂ product, such as CaloMist. Noncompliance or inadequate treatment with vitamin B₁₂ therapy may result in recurrence of anemia and the development or worsening of irreversible neurological damage.

The dosing of CaloMist and other intranasal medications should be separated by several hours.

Vitamin B₁₂ concentrations should be monitored one month after CaloMist initiation or dose change and every 3-6 months thereafter.

Careful instructions on the priming of the actuator and nasal administration of CaloMist should be given to the patient, and the procedures for use should be demonstrated.

17.2 Patient Instruction Sheet

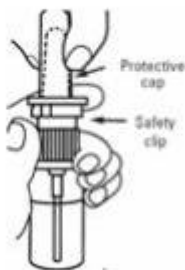
Instructions for Using CaloMist. Read the following instructions carefully before using CaloMist.

- Use **CaloMist** as directed by your doctor.

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

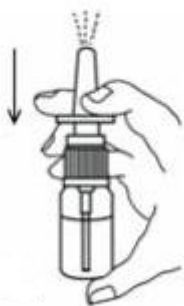
CaloMist Pump Priming: Before you use the medicine for the first time the nasal spray pump unit must be readied (primed).

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 CaloMist with two re-priming sprays if you do not use for five days or more.
Your CaloMist 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. Place your thumb on the bottom of the bottle. (See *Diagram 4*)
3. Gently insert the nasal spray pump into 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. Firmly and quickly press down the arms of the nasal spray bottle.
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. After use, wipe the nozzle of the nasal spray pump with a clean tissue. Replace the safety clip and clear cover on the nasal spray pump.
8. Store CaloMist upright at room temperature, 15° - 30° C (59° - 86° F). Do not freeze.

Discard CaloMist 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 CaloMist and all medicines out of the reach of children.

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