

## 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 nasal spray)

Initial U.S. Approval: 1942

### INDICATIONS AND USAGE

CaloMist is a vitamin B<sub>12</sub> indicated for:

- Maintenance of vitamin B<sub>12</sub> concentrations after normalization with intramuscular vitamin B<sub>12</sub> therapy in patients with vitamin B<sub>12</sub> deficiency who have no nervous system involvement (1.1)

### Limitations of Use

CaloMist has not been evaluated for the treatment of newly diagnosed vitamin B<sub>12</sub> 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)
- Patients with vitamin B<sub>12</sub> deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B<sub>12</sub> therapy (8.6)

### DOSAGE FORMS AND STRENGTHS

- Nasal spray: 25 mcg cyanocobalamin, USP /0.1 mL (3)

### CONTRAINDICATIONS

- Sensitivity to cobalt, vitamin B<sub>12</sub>, or any component of this product (4)

### WARNINGS AND PRECAUTIONS

- Laboratory Monitoring: Monitor Vitamin B<sub>12</sub> concentrations before and during treatment. Switch back to intramuscular dosing for patients with declining or abnormally low vitamin B<sub>12</sub> concentrations. (5.1)
- Use in Patients with Nasal Pathology: Effectiveness in patients with nasal pathology or with other concomitant intranasal drugs has not been determined. Use with caution. (5.2)
- Use in Patients with Leber's Disease: 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<sub>12</sub> 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](http://www.fda.gov/medwatch)

### See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2020

## FULL PRESCRIBING INFORMATION: CONTENTS \*

### 1 INDICATIONS AND USAGE

- 1.1 Vitamin B<sub>12</sub> Maintenance Therapy
- 1.2 Limitations of Use

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Priming (Activation) of Pump

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Laboratory Monitoring
- 5.2 Use in Patients With Nasal Pathology
- 5.3 Use in Patients with Leber's Disease
- 5.4 Anaphylaxis and Angioedema
- 5.5 Megaloblastic Anemia
- 5.6 Blunted Response to Vitamin B<sub>12</sub> Therapy

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Experience with Parenteral Vitamin B<sub>12</sub>
- 6.3 Postmarketing Experience

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use+
- 8.6 Renal/Hepatic Impairment

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Vitamin B<sub>12</sub> Maintenance Therapy

CaloMist is indicated for maintenance of vitamin B<sub>12</sub> concentrations after normalization with intramuscular vitamin B<sub>12</sub> therapy in patients with vitamin B<sub>12</sub> deficiency who have no nervous system involvement.

#### 1.2 Limitations of Use

CaloMist has not been evaluated for the treatment of newly diagnosed vitamin B<sub>12</sub> deficiency.

CaloMist is not suitable for use in the vitamin B<sub>12</sub> 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 Dosage

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 B<sub>12</sub> 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.

Refer to *Patient Labeling (Instructions for Use)* for detailed information.

### 3 DOSAGE FORMS AND STRENGTHS

Nasal Spray: 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 of cyanocobalamin in a 0.1 mL of solution per spray. 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

CaloMist is contraindicated in patients with sensitivity to cobalt, vitamin B<sub>12</sub>, or any component of this product. Reactions following administration of parenteral vitamin B<sub>12</sub> have included: anaphylactic shock, death, and angioedema [*see Warnings and Precautions (5.4)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Laboratory Monitoring

Obtain hematocrit, reticulocyte count, vitamin B<sub>12</sub>, folate, and iron levels prior to treatment. All hematologic parameters, including vitamin B<sub>12</sub> concentrations, should be normal before initiating treatment with CaloMist. Monitor serum vitamin B<sub>12</sub> concentrations periodically to confirm adequacy of therapy. Monitor Vitamin B<sub>12</sub> concentrations and complete blood counts one month after starting CaloMist and then at 3 to 6 month intervals thereafter. Monitor methylmalonic acid and homocysteine concentrations in patients with borderline-low vitamin B<sub>12</sub> concentrations (<300 ng/L) as these are more sensitive measures of vitamin B<sub>12</sub> deficiency in this setting. Switch back to intramuscular route of administration for patients with declining or abnormally low vitamin B<sub>12</sub> concentrations despite maximal doses of CaloMist. Vitamin B<sub>12</sub> 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. In patients with nasal pathology, defer treatment with CaloMist until nasal symptoms have subsided. Patients with chronic nasal symptoms or significant nasal pathology are not ideal candidates for intranasal vitamin B<sub>12</sub> therapy. If CaloMist therapy is attempted in these patients, monitor vitamin B<sub>12</sub> concentrations 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 is not recommended for use 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 B<sub>12</sub> administration.

#### 5.5 Megaloblastic Anemia

Megaloblastic anemia has many causes, including vitamin B<sub>12</sub> deficiency and folate deficiency. Folic acid may result in a hematological response in patients with vitamin B<sub>12</sub> deficiency but will not prevent irreversible neurological manifestations. Vitamin B<sub>12</sub> 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<sub>12</sub>. Monitor serum potassium and platelet counts more frequently in this setting.

#### 5.6 Blunted Response to Vitamin B<sub>12</sub> 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<sub>12</sub> 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 B<sub>12</sub> 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 B<sub>12</sub> levels with intramuscular vitamin B<sub>12</sub> 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 B<sub>12</sub> concentrations.

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

Adverse Reaction	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 B<sub>12</sub>:

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)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Administration of the approved recommended dose of CaloMist is not expected to cause major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with CaloMist nasal spray. There are risks associated with vitamin B<sub>12</sub> deficiency during pregnancy (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo/fetal risk*

Severe maternal vitamin B<sub>12</sub> deficiency during pregnancy may result in adverse pregnancy outcomes such as low birth weight, preterm birth and megaloblastic anemia.

### 8.2 Lactation

#### Risk Summary

Vitamin B<sub>12</sub> is present in human milk. Administration of the approved recommended dose of CaloMist is not expected to cause harm to a breastfed child. There is no information on the effects of CaloMist on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CaloMist and any potential adverse effects on the breastfed infant from the underlying maternal condition.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 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.

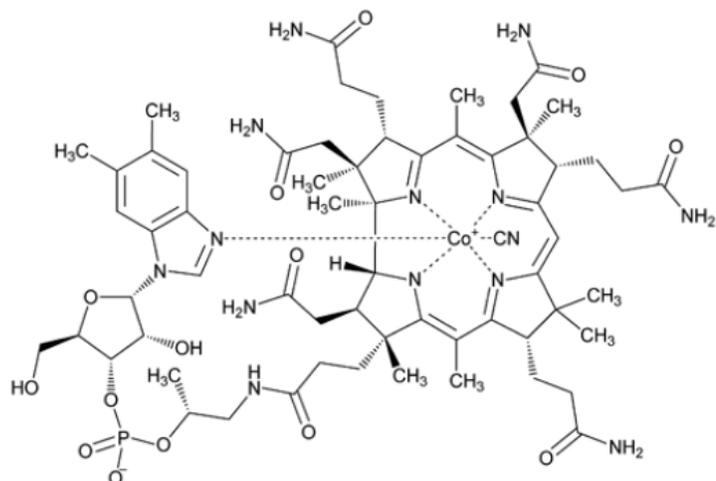
### 8.6 Renal/Hepatic Impairment

Patients with vitamin B<sub>12</sub> deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of vitamin B<sub>12</sub> therapy.

## 11 DESCRIPTION

CaloMist contains cyanocobalamin. Cyanocobalamin is a synthetic form of vitamin B<sub>12</sub> with activity equivalent to the endogenous form of vitamin B<sub>12</sub>. The chemical name of Cyanocobalamin is Vitamin B<sub>12</sub>. 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<sub>12</sub> coenzymes are very unstable in light.

Each spray of CaloMist contains 25 mcg of cyanocobalamin, sodium chloride, sodium phosphate monobasic, benzyl alcohol, sodium hydroxide, and benzalkonium chloride in purified water with an attached spray pump unit. CaloMist spray solution has a pH between 6.5 and 7.5.

## 12 CLINICAL PHARMACOLOGY

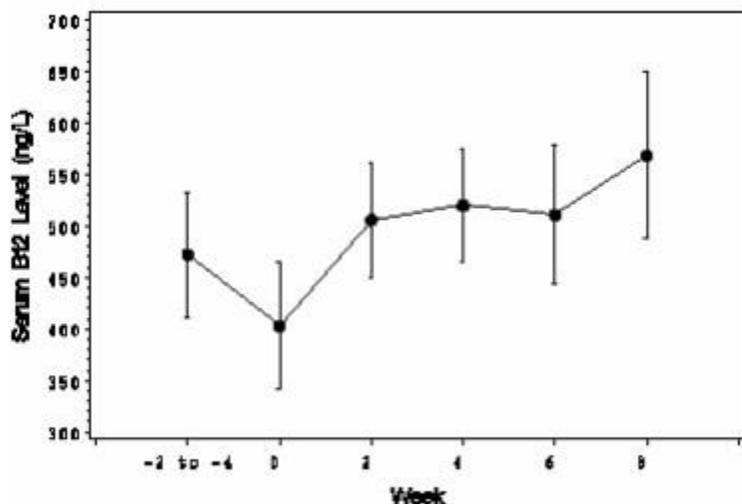
### 12.1 Mechanism of Action

Vitamin B<sub>12</sub> 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<sub>12</sub>. In tissues, vitamin B<sub>12</sub> is essential for the conversion of methylmalonate to succinate and for the synthesis of methionine from homocysteine. In the absence of vitamin B<sub>12</sub>, tetrahydrofolate cannot be regenerated from 5-methyl tetrahydrofolate, and functional folate deficiency occurs. Vitamin B<sub>12</sub> 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<sub>12</sub> deficient patients who were stabilized on intramuscular (IM) vitamin B<sub>12</sub> therapy, once daily intranasal dosing with CaloMist for 8 weeks resulted in serum vitamin B<sub>12</sub> 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<sub>12</sub> (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 B<sub>12</sub> concentrations. One of the 25 patients dosed with CaloMist was excluded from the efficacy analyses because a diagnosis of vitamin B<sub>12</sub> deficiency could not be confirmed.

**Figure 1. Mean Vitamin B<sub>12</sub> Serum Levels Over 8 Weeks of Intranasal (IN) Vitamin B<sub>12</sub> Dosing in 24 Subjects Stabilized on Intramuscular (IM) Vitamin B<sub>12</sub>**



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 B<sub>12</sub> serum levels with 95% confidence intervals.

### 12.3 Pharmacokinetics

#### Distribution

In the blood, vitamin B<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> is administered in doses that saturate the binding capacity of plasma proteins and the liver, the unbound vitamin B<sub>12</sub> is rapidly eliminated in the urine. Retention of vitamin B<sub>12</sub> 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<sub>12</sub> products, including CaloMist. There is no evidence from long-term use in patients with pernicious anemia that vitamin B<sub>12</sub> 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<sub>12</sub>.

No studies have been performed to evaluate the potential of CaloMist for genotoxicity.

Animal reproduction studies assessing the effects of CaloMist on male and female fertility have not been conducted.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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. 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 0.1 mL of spray solution. One bottle delivers thirty 50 mcg doses (60 sprays) (NDC 0256-0203-01).

#### Storage

Store upright at room temperature between 59 °F to 86 °F (15 °C to 30 °C).

Protect from heat and light.

Protect from freezing.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use)

### Important Information for Patients

- Advise patients with a chronic underlying cause of vitamin B<sub>12</sub> deficiency that they will require indefinite administration of a vitamin B<sub>12</sub> product, such as *CaloMist*. Noncompliance or inadequate treatment with vitamin B<sub>12</sub> therapy may result in recurrence of anemia and the development or worsening of irreversible neurological damage.
- Advise patients to separate the dosing of *CaloMist* and other intranasal medications by several hours.
- Advise patients that Vitamin B<sub>12</sub> levels will be monitored one month after *CaloMist* initiation or dose change and every 3-6 months thereafter.
- Instruct patients on how to prime the actuator and administer the dose of *CaloMist*. Have the patient demonstrate the administration procedure.

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