CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-722/S004

Trade Name: Nascobal Gel for Intranasal Administration

Generic Name: (cyanocobalamin, USP)

Sponsor: Nastech Pharmaceutical Company, Inc.

Approval Date: June 14, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-722/S004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Medical Review(s)	
Chemistry Review(s)	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-722/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-722/S-004

Nastech Pharmaceutical Co.
Attention: Peter C. Aprile, R.Ph.
Senior Director, Regulatory and Quality Affairs
Corporate Headquarters
45 Adams Avenue
Hauppauge, NY 11788

Dear Mr. Aprile:

Please refer to your supplemental new drug application dated December 20, 2001, received December 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nascobal (cyanocobalamin, USP) Gel for Intranasal Administration.

We acknowledge receipt of your submission dated February 2, 2002.

This supplemental new drug application provides for revision of the INDICATIONS AND USAGE section of the package insert to add HIV infection, AIDS, and Crohn's disease to the list of conditions which could result in Vitamin B12 deficiency and for which Nascobal would be indicated.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the package insert submitted February 2, 2002.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-722/S-004." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care

Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Kati Johnson
6/14/02 02:39:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-722/S004

LABELING

PC3137B

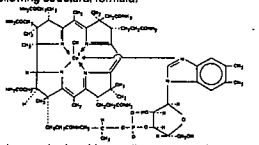
nascobal®
(Cyanocobalamin, USP)
Gel for Intranasal Administration
500 mcg/0.1 mL
Rx Only

PC3137B

nascobal®
(Cyanocobalamin, USP)
Gel for Intranasal Administration
500 mcg/0.1 mL
Rx Only

DESCRIPTION

Cyanocobalamin is a synthetic form of vitamin B_{12} with equivalent vitamin B_{12} activity. The chemical name is 5,6-dimethyl-benzimidazolyl 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 1355.38 and the following structural formula:



Cyanocobalamin occurs as dark red crystals or orthorhombic needles or crystalline red powder. It is very hygroscopic in the anhydrous form, and sparingly to moderately soluble in water (1:80). Its pharmacologic activity 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.

NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is a solution of Cyanocobalamin, USP (vitamin B_{12}) for administration as a metered gel to the nasal mucosa. Each bottle of NASCOBAL® contains 2.3 mL of a 500 mcg/0.1 mL gel solution of cyanocobalamin with methylcellulose, sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water. The gel solution has a pH between 4.5 and 5.5. The gel pump unit must be fully primed (see Patient Instructions) prior to initial use. After initial priming, each metered gel delivers an average of 500 mcg of cyanocobalamin and the 2.3 mL of gel contained in the bottle will deliver 8 doses of NASCOBAL®, if the unit is kept upright, reprimingbetween doses should not be necessary (see Patient Instructions).

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION

Vitamin B_{12} is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (e.g., epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for vitamin B_{12}. Vitamin B_{12} can be converted to coenzyme B_{12} in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. In the absence of coenzyme B_{12}, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyl tetrahydrofolate, and a functional folate deficiency occurs. Vitamin B_{12} also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B_{12} is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B_{12} deficiency results in megaloblastic anemia, GI lesions, and neurologic damage that begins with an inability to produce myelin and is followed by gradual degeneration of the axon and nerve head.

Cyanocobalamin is the most stable and widely used form of vitamin B_{12}, and has hematopoietic activity apparently identical to that of the antianemia factor in purified liver extract. The information below, describing the clinical pharmacology of cyanocobalamin, has been derived from studies with injectable vitamin B_{12}.

Vitamin B_{12} is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection. It is bound to plasma proteins and stored in the liver. Vitamin B_{12} is excreted in the bile and undergoes some enterohepatic recycling. Absorbed vitamin B_{12} is transported via specific B_{12} binding proteins, transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B_{12} storage.

Parenteral (intramuscular) administration of vitamin B_{12} completely reverses the megaloblastic anemia and GI symptoms of vitamin B_{12} deficiency; the degree of improvement in neurologic symptoms depends on the duration and severity of the lesions, although progression of the lesions is immediately arrested.

Gastrointestinal absorption of vitamin B_{12} depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B_{12} prevents progression of neurologic damage.

The average diet supplies about 4 to 15 mcg/day of vitamin B_{12} in a protein-bound form that is available for absorption after normal digestion. Vitamin B_{12} is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B_{12} enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B_{12}.

Colchicine, para-aminosalicylic acid, and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

PHARMACOKINETICS

Absorption

In a bioavailability study in 24 pernicious anemia patients comparing B_{12} nasal gel to intramuscular B_{12}, peak concentrations of B_{12} after intranasal administration were reached in 1-2 hours. The average peak concentration of B_{12} after intranasal administration was 1,414 ± 1,003 pg/mL. The bioavailability of the nasal gel relative to an intramuscular injection was found to be 8.9% (90% confidence intervals 7.1-11.2%).

In pernicious anemia patients, once weekly intranasal dosing with 500 mcg B_{12} resulted in a consistent increase in pre-dose serum B_{12} levels during one month of treatment ($p < 0.003$) above that seen one month after 100 mcg intramuscular dose (Figure).

Distribution

In the blood, B_{12} is bound to transcobalamin II, a specific B-globulin carrier protein, and is distributed and stored primarily in the liver and bone marrow.

Elimination

About 3-8 mcg of B_{12} is secreted into the GI tract daily via the bile; in normal subjects with sufficient intrinsic factor, all but about 1 mcg is re-absorbed. When B_{12} is administered in doses which saturate the binding capacity of plasma proteins and the liver, the unbound B_{12} is rapidly eliminated in the urine. Retention of B_{12} in the body is dose-dependent. About 80-90% of an intramuscular dose up to 50 mcg is retained in the body; this percentage drops to 55% for a 100 mcg dose, and decreases to 15% when a 1000 mcg dose is given.

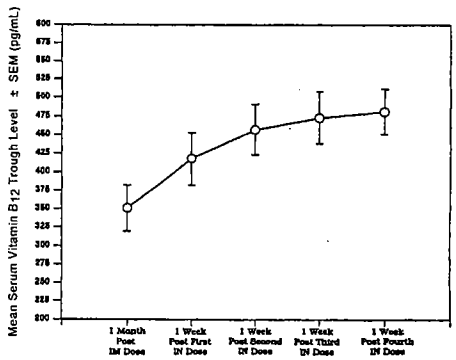


Figure. Vitamin B_{12} Serum Trough Levels After Intramuscular Solution (IM) of 100 mcg and Nasal Gel (IN) Administration of 500 mcg Cyanocobalamin After Weekly Doses.

INDICATIONS AND USAGE

NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is indicated for the maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B_{12} therapy for the following conditions:

I. Pernicious anemia, indicated only in patients who are in hematologic remission with no nervous system involvement.
II. Dietary deficiency of vitamin B_{12} occurring in strict vegetarians (isolated vitamin B_{12} deficiency is very rare.)
III. Malabsorption of vitamin B_{12} resulting from structural or functional damage to the stomach, where intrinsic factor is secreted, or to the ileum, where intrinsic factor facilitates vitamin B_{12} absorption. These conditions include HIV infection, AIDS, Crohn's disease, tropical sprue, and nontropical sprue (idiopathic steatorrhea, gluten-induced enteropathy). Folate deficiency in these patients is usually more severe than vitamin B_{12} deficiency.
IV. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis, HIV infection, AIDS, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B_{12} deficiency. Structural lesions leading to vitamin B_{12} deficiency include regional ileitis, ileal resections, malignancies, etc.
V. Competition for vitamin B_{12} by intestinal parasites or bacteria. The fish tapeworm (Diphyllobothrium latum) absorbs huge quantities of vitamin B_{12} and infested patients often have associated gastric atrophy. The blind loop syndrome may produce deficiency of vitamin B_{12} or folate.
VI. Inadequate utilization of vitamin B_{12}. This may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see "Drug/Laboratory Test Interactions"), use a gluten free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B_{12}.

Requirements of vitamin B_{12} in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with intranasal or oral supplementation.

NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration has only been tested in patients with vitamin B_{12} malabsorption who have received prior intramuscular cyanocobalamin treatment and are in hematologic remission.

NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is not suitable for vitamin B_{12} absorption test (Schilling Test).

CONTRAINDICATION

Sensitivity to cobalt and/or vitamin B_{12} or any component of the medication is a contraindication.

WARNINGS

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B_{12} suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Folic acid is not a substitute for vitamin B_{12} although it may improve vitamin B_{12}-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B_{12}-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

Anaphylactic shock and death have been reported after parenteral vitamin B_{12} administration. No such reactions have been reported in clinical trials with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration.

Blunted or impeded therapeutic response to vitamin B_{12} may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

Nastech Nascobal Rev. 2/99 Size: 11 x 8-1/2 Type Size: 5.75 pt Front 12-20-01 JB

PC3137B

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PRECAUTIONS

1. GENERAL

An intradermal test dose of parenteral vitamin B_{12} is recommended before NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is administered to patients suspected of cyanocobalamin sensitivity. Vitamin B_{12} deficiency that is allowed to progress for longer than three months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B_{12} deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B_{12}, irreversible damage will result.

Doses of vitamin B_{12} exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

The validity of diagnostic vitamin B_{12} or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

Vitamin B_{12} is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B_{12} could mask the true diagnosis.

Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B_{12} therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.

Vitamin B_{12} deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B_{12} may unmask this condition.

If a patient is not properly maintained with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration, intramuscular vitamin B_{12} is necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy.

The effectiveness of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Therefore, treatment with NASCOBAL® should be deferred until symptoms have subsided.

2. INFORMATION FOR PATIENTS

Patients with pernicious anemia should be instructed that they will require weekly intranasal administration of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B_{12}, because the former may prevent anemia but allow progression of subacute combined degeneration of the spinal cord.

(Hot foods may cause nasal secretions and a resulting loss of medication; therefore, patients should be told to administer NASCOBAL® at least one hour before or one hour after ingestion of hot foods or liquids).

A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B_{12}. Therefore, patients following such a diet should be advised to take NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration weekly. The need for vitamin B_{12} is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

The patient should also understand the importance of returning for follow-up blood tests every 3 to 6 months to confirm adequacy of the therapy. Careful instructions on the actuator assembly, priming of the actuator and nasal administration of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient.

3. LABORATORY TESTS

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. If folate levels are low, folic acid should also be administered. All hematologic parameters should be normal when beginning treatment with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration.

Vitamin B_{12} blood levels and peripheral blood counts must be monitored initially at one month after the start of treatment with NASCOBAL®, and then at intervals of 3 to 6 months.

A decline in the serum levels of B_{12} after one month of treatment with B_{12} nasal gel may indicate that the dose may need to be adjusted upward. Patients should be seen one month after each dose adjustment; continued low levels of serum B_{12} may indicate that the patient is not a candidate for this mode of administration.

Patients with pernicious anemia have about 3 times the incidence of carcinoma of the stomach as in the general population, so appropriate tests for this condition should be carried out when indicated.

4. DRUG/LABORATORY TEST INTERACTIONS

Persons taking most antibiotics, methotrexate or pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

5. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential have not been done. 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 is believed to be related to the underlying pathology and not to treatment with vitamin B_{12}.

6. PREGNANCY

Pregnancy Category C: Animal reproduction studies have not been conducted with vitamin B_{12}. It is also not known whether vitamin B_{12} can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B_{12} is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science - National Research Council for pregnant women should be consumed during pregnancy.

7. NURSING MOTHERS

Vitamin B_{12} appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B_{12} blood level. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women should be consumed during lactation.

8. PEDIATRIC USE

Intake in pediatric patients should be in the amount recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

ADVERSE REACTIONS

The incidence of adverse experiences described in the Table below are based on data from a short-term clinical trial in vitamin B_{12} deficient patients in hematologic remission receiving NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration (N=24) and intramuscular vitamin B_{12} (N=25).

Table Adverse Experiences by Body System, Number of Patients and Number of Occurrences by Treatment Following Intramuscular and Intranasal Administration of Cyanocobalamin.

Body System	Adverse Experience	Number of Patients (Occurrences)	
		Vitamin B_{12} Nasal Gel, 500 mcg N=24	Intramuscular Vitamin B_{12}, 100 mcg N=25
Body as a Whole	Asthenia	1 (1)	4 (4)
	Back Pain	0 (0)	1 (1)
	Generalized Pain	0 (0)	2 (3)
	Headache	1 (2)*	5 (11)
	Infection[a]	3 (4)	3 (3)
Cardiovascular System	Peripheral Vascular Disorder	0 (0)	1 (1)
Digestive System	Dyspepsia	0 (0)	1 (2)
	Glossitis	1 (1)	0 (0)
	Nausea	1 (1)*	1 (1)
	Nausea & Vomiting	0 (0)	1 (1)
	Vomiting	0 (0)	1 (1)
Musculoskeletal System	Arthritis	0 (0)	2 (2)
	Myalgia	0 (0)	1 (1)
Nervous System	Abnormal Gait	0 (0)	1 (1)
	Anxiety	0 (0)	1 (1)*
	Dizziness	0 (0)	3 (3)
	Hypoesthesia	0 (0)	1 (1)
	Incoordination	0 (0)	1 (2)*
	Nervousness	0 (0)	1 (3)*
	Paresthesia	1 (1)	1 (1)
Respiratory System	Dyspnea	0 (0)	1 (1)
	Rhinitis	1 (1)*	2 (2)

[a] Sore throat, common cold

* There may be a possible relationship between these adverse experiences and the study drugs. These adverse experiences could have also been produced by the patient's clinical state or other concomitant therapy.

The intensity of the reported adverse experiences following the administration of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B_{12} were generally mild. One patient reported severe headache following intramuscular dosing. Similarly, a few adverse experiences of moderate intensity were reported following intramuscular dosing (two headaches and rhinitis; one dyspepsia, arthritis, and dizziness), and dosing with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration (one headache, infection, and paresthesia).

The majority of the reported adverse experiences following dosing with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B_{12} were judged to be intercurrent events. For the other reported adverse experiences, the relationship to study drug was judged as "possible" or "remote". Of the adverse experiences judged to be of "possible" relationship to the study drug, anxiety, incoordination, and nervousness were reported following intramuscular vitamin B_{12} and headache, nausea, and rhinitis were reported following dosing with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration.

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

Generalized: Anaphylactic shock and death (See Warnings and Precautions).
Cardiovascular: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.
Hematological: Polycythemia vera.
Gastrointestinal: Mild transient diarrhea.
Dermatological: Itching; transitory exanthema.
Miscellaneous: Feeling of swelling of the entire body.

OVERDOSAGE

No overdosage has been reported with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration or parenteral vitamin B_{12}.

DOSAGE AND ADMINISTRATION

The recommended initial dose of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration in patients with vitamin B_{12} malabsorption who are in remission following injectable vitamin B_{12} therapy is 500 mcg administered intranasally once weekly. Patients should be in hematologic remission before treatment with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration.

See LABORATORY TESTS for monitoring B_{12} levels and adjustment of dosage.

HOW SUPPLIED

NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is available as a metered dose gel in 5 mL glass bottles containing 2.3 mL of gel. It is available in a dosage strength of 500 mcg per actuation (0.1 mL/actuation). A screw-on actuator is provided. This actuator, following priming, will deliver 0.1 mL of the gel. NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is provided in a sealed prescription vial containing a metered dose nasal gel actuator with dust cover, a bottle of nasal gel solution, and a patient instruction leaflet. One bottle will deliver 8 doses (NDC 0091-7033-13).

PHARMACIST ASSEMBLY INSTRUCTIONS FOR NASCOBAL® (CYANOCOBALAMIN, USP) GEL FOR INTRANASAL ADMINISTRATION

The pharmacist should assemble NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration prior to dispensing to the patient, according to the following instructions:

1. Break the protective seal, open the prescription vial, and remove the gel actuator and gel solution bottle.
2. Assemble NASCOBAL® by first unscrewing the white cap from the gel solution bottle and screwing the actuator unit lightly onto the bottle. Make sure the clear dust cover is on the pump unit.
3. Return the NASCOBAL® bottle to the prescription vial for dispensing to the patient.

STORAGE CONDITIONS

Protect from light. Keep covered in prescription vial until ready to use. Store upright at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.

Mfd. by Nastech Pharmaceutical Company Inc.
Hauppauge, NY 11788
PC3137B
Rev. 12/01

Distr. by Schwarz Pharma, Inc.
Milwaukee, WI 53201

Nastech Nascobal Rev. 2/99 Size: 11 x 8-1/2 Type Size: 5.75 pt Back 12-20-01 JB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-722/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-722/S-004

Nastech Pharmaceutical Company, Inc.
Attention: Peter Aprile. RPh
V.P., Regulatory and Quality Affairs
45 Adams Avenue
Hauppauge, NY 11731

Dear Mr. Aprile:

We acknowledge receipt of your September 4, 2002 submission containing final printed labeling in response to our June 14, 2002 letter approving your supplemental new drug application for Nascobal Gel for Intranasal Administration (cyanocobalamin, USP).

We have reviewed the labeling that you submitted in accordance with our June 14, 2002 letter and we find it acceptable.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
1/14/03 06:00:54 AM
signing for David Orloff, MD

Division of Metabolic & Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-722/S-004

Name of Drug: Nascobal (cyanocobalamine, USP) Gel for Intranasal Administration

Applicant: Nastech Pharmaceutical Company, Inc.

Material Reviewed:

Submission Date(s): September 4, 2002, Final Printed Labeling (FPL), Package Insert (PI)

Receipt Date(s): September 5, 2002

Background and Summary

Nascobal is currently approved for the maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B-12 therapy for multiple conditions.

Supplement –004 was submitted December 20, 2001 and provides for revision of the INDICATIONS AND USAGE section of the package insert to add HIV infection, AIDS, and Crohn's disease to the list of conditions which could result in Vitamin B-12 deficiency and for which Nascobal would be indicated. The application was approved on draft labeling on June 14, 2002, and the firm has now submitted final printed labeling.

Review

The FPL (Identifier PC3137B, Revised 12/01) was compared to the draft labeling upon which the supplement was approved. They are identical.

Conclusions

An ACK and RETAIN letter should be issued. The currently approve PI for NDA 19-722 is **Identifier PC3137B, Revised 12/01.**

Kati Johnson, Chief, PM Staff, HFD-510

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/s/

Kati Johnson
1/14/03 05:56:35 AM
CSO

Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 19-722/S-004

Name of Drug: Nascobal (cyanocobalamin, USP) Gel for Intranasal Administration

Sponsor: Nastech Pharmaceuticals Corp

Material Reviewed:

Submission Date(s): 12/20/01, draft labeling, package insert (PI)
2/6/02, revised labeling

Background and Summary

Nascobal is currently approved for the maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B12 therapy for a variety of conditions.

Supplemental application –004 was submitted to add HIV infection, AIDS, and Crohn's disease to the existing list of examples of diseases which could result in vitamin B12 deficiency and for which Nascobal would be indicated. This submission was based on a telecon held with the firm on November 1, 2001.

Review

The proposed PI (**PC3137B, Rev. 12/01**) was compared to the currently approved PI (**Identifier, PC3137A, Rev. 12/98, approved with S-001 on June 22, 1999**). The INDICATIONS section has been revised as follows (underlined wording has been added):

III. Malabsorption of vitamin B_{12} resulting from structural or functional damage to the stomach, where intrinsic factor is secreted, or to the ileum, where intrinsic factor facilitates vitamin B_{12} absorption. These conditions include HIV infection, AIDS, Crohn's disease, tropical sprue, and nontropical sprue (idiopathic steatorrhea, gluten-induced enteropathy). Folate deficiency in these patients is usually more severe than vitamin B_{12} deficiency.

IV. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis,HIV infection, AIDS, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B_{12}

deficiency. Structural lesions leading to vitamin B_{12} deficiency include regional ileitis, ileal resections, malignancies, etc.

The rest of the PI is identical.

Conclusions

According to Dr. Mary Parks, MD, Deputy Division Director, the literature references that were included in the application adequately support the proposed revisions.

An Approval letter on draft labeling should be drafted, and the firm requested to submit final printed labeling.

Kati Johnson
Chief, Project Management Staff, HFD-510

Drafted: Kjohnson.6/12/02
Revised/Initialed:
Finalized:KJ 6/13/02
Filename: c:\labeling\nascobals04rev.doc

PM LABELING REVIEW

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/s/

Kati Johnson
6/14/02 02:25:29 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA19-722/S-004

Nastech Pharmaceutical Company Inc.
Attention: Peter C. Aprile
Senior Director, Regulatory and Quality Affairs
45 Adams Avenue
Hauppauge, NY 11788

Dear Mr. Aprile:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration

NDA Number: 19-722

Supplement Number: S-004

Date of Supplement: December 20, 2001

Date of Receipt: December 21, 2001

This supplement proposes labeling revisions to the **INDICATIONS AND USAGE** section of the package insert to include additional examples of diseases which could result in Vitamin B_{12} deficiency, This application was be filed under section 505(b) of the Act on February 19, 2002, in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

Steve McCort
Regulatory Project Manager
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Stephen McCort
3/15/02 08:56:07 AM