Cyanocobalamin occurs as dark red crystals or amorphous needles or crystalline red powder. It is very hygroscopic in the anhydrous form, and sparingly to moderately soluble in water (180). 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 B12 coenzymes are very unstable in light.

Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. Each bottle of Nascobal Nasal Spray contains 2.3 mL of a single strength solution of cyanocobalamin (vitamin B12) with sodium chloride in purified water. The spray solution has a pH between 4.5 and 5.5. The spray pump unit must be fully primed (see Dosage and Administration) prior to initial use. After initial priming, each spray delivers an average of 500 mcg of cyanocobalamin and the 2.3 mL of spray solution contained in the bottle will deliver 8 doses of Nascobal Nasal Spray. The unit must be re-primed before each dose. (see Dosage and Administration).

PHARMACOKINETICS

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION

Vitamin B12 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 B12. Vitamin B12 can be converted to cyanocobalamin in tissues, and as such is essential for conversion of methionine to cysteine and synthesis of methionine from homocysteine, a reaction which also requires folic acid. In the absence of cyanocobalamin, thymidylate cannot be regenerated from its inactive storage form, 5-methyltetrahydrofolate, and a functional folate deficiency occurs. Vitamin B12 also may be involved in maintaining sulfahydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B12 is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B12 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 axons that make up the nerve head.

Cyanocobalamin is the most stable and widely used form of vitamin B12, 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 B12.

Vitamin B12 is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection. It is bound to plasma proteins and stored in the liver. Vitamin B12 is excreted in the bile and undergoes enterohepatic recycling. Absorbed vitamin B12 is transported via specific B12-binding proteins: transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B12 storage.

Parenteral (intramuscular) administration of vitamin B12 completely reverses the megaloblastic anemia and GI symptoms of vitamin B12 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 B12 depends on the presence of sufficient intrinsic factor and calcium (or). Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B12 prevents progression of neurologic damage.

The average diet supplies about 4 to 15 mcg of vitamin B12 in a protein-bound form that is available for absorption after normal digestion. Vitamin B12 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 milk or milk products).

Vitamin B12 is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B12 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 large doses. The absorption is considered too unpredictable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B12.

Cobalamin, para-aminocobalamin, and heavy alcohol intake longer than 2 weeks may produce malabsorption of vitamin B12.

PHARMACOKINETICS

Absorption

A three-way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B12 nasal spray to the B12 nasal gel and to establish the relative bioavailability of the nasal formulations to the intramuscular injection. The peak concentrations after administration of intranasal spray were reached in 1.25 ± 1.9 hours. The average peak concentration of B12 obtained after baseline correction following administration of intranasal spray was 757.86 ± 532.17 pg/mL. The bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%. The bioavailability of the B12 nasal spray was found to be 10% less than the B12 nasal gel. The 90% confidence interval for the log10-transformed AUC of the nasal spray was 77.11% ± 114.19% and 71.6% ± 118.06% respectively.

In pernicious anemia patients, once weekly intranasal dosing with 500 mcg B12 gel resulted in a consistent increase in pre-dose serum B12 levels following administration of intranasal spray was 757.96 ± 532.17 pg/mL. The bioavailability of the nasal spray relative to the intramuscular spray was found to be 6.1%.

Elimination

About 38 mcg of B12 is secreted into the GI tract daily via the bile in normal subjects with sufficient intrinsic factor, but all about 1 mcg is re-absorbed. When B12 is administered in doses that saturate the binding capacity of plasma proteins and the liver, the unbound B12 is rapidly excreted by the kidneys. Retention of B12 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 5% for a 100 mcg dose, and decreases to 15% when a 1000 mcg dose is given.

Figure. Vitamin B12 Serum Total Levels After Intramuscular Injection (IM) of 100 mcg and Nasal Gel (IN) Administration of 500 mcg Cyanocobalamin After Weekly Dosage

INDICATIONS AND USAGE

Nascobal® Nasal Spray is indicated for the maintenance of normal hematopoietic status in pernicious anemia patients who are in remission following intramuscular vitamin B12 therapy and who have no systemic involvement.

Nascobal® Nasal Spray is also indicated as a supplement for other vitamin B12 deficiencies, including:

1. Dietary deficiency of vitamin B12 occurring in strict vegetarians (isolated vitamin B12 deficiency is very rare).
2. Malabsorption of vitamin B12 resulting from structural or functional intestinal injury, or isolated to the ileum. The intrinsic factor facilitates vitamin B12 absorption. The 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 B12 deficiency.
3. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (erosion of gastritis, 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 B12 deficiency. Structural lesions leading to vitamin B12 deficiency include regional ileitis, ileal resections, malignancies, etc.
4. Competition for vitamin B12 by intestinal parasites or bacteria. The fish tapeworm (Diphyllobothrium latum) absorbs huge quantities of vitamin B12 and infected patients often have associated gastric atrophy. The blind loop syndrome may produce deficiency of vitamin B12 or folic acid.

Intranasal administration of vitamin B12 may occur if analine deficiency 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 of a gluten free diet in nontropical sprue, eradication of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B12.

Requirements of vitamin B12 in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemmorhage, hepatic and renal disease) cannot be met with intranasal or oral supplementation.

Nascobal® Nasal Spray is not suitable for vitamin B12 absorption test (Schilling Test).
ADVERSE EXPERIENCES by Body System, Number of Patients and Number of Occurrences by Treatment Following Intramuscular nascobal

The effectiveness of Nascobal Nasal Spray in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Therefore, treatment with Nascobal Nasal Spray should be deferred until symptoms have subsided.

The intensity of the reported adverse experiences following the administration of Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B12 were generally mild. One case of anaphylactic shock and death (see Warnings and Precautions) has been reported following intranasal administration of Nascobal Nasal Spray.

The majority of the reported adverse experiences following dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B12 were judged to be intercurrent events. For the other reported adverse experiences, the relationship to study drug was assessed and rated 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 B12 and headache, nausea, and rhinitis were reported following dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration.

The following adverse reactions have been observed following parenteral vitamin B12:

Generalized: Anaphylactic shock and death (See Warnings and Precautions).

Cardiovascular: Palpitations with chest distress.

Gastrointestinal: Nausea and vomiting.

Dermatologic: Transient vasodilatation.

Miscellaneous: Feeling of swelling of the entire body.

OVERDOSE
No experience has been reported following intranasal vitamin B12 doses.

DOSAGE AND ADMINISTRATION
The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in one nostril once weekly. Nascobal Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids. Periodic monitoring of serum B12 levels should be obtained to establish adequacy of therapy.

Priming (Activation) of Pump

1. Before the first dose and administration, the pump must be primed. To prime the pump, place muzzle between the first and second finger with the thumb on the bottom of the bottle. Pump the unit firmly and quickly until the first appearance of spray. Then prime the pump an additional 2 times. Now the nasal spray is ready for use. The unit must be re-primed before each dose. Primes the pump immediately before each administration of doses 2 through 8. See LABORATORY TESTS for monitoring B12 levels and adjustment of dosage.

HOW SUPPLIED
Nascobal Nasal Spray is available as a spray in 3 mL glass bottles containing 2.3 mL of solution. It is available in a dosage strength of 500 mcg per actuation (0.1 mL). A screw-on actuator is provided. This actuator, following priming, will deliver 0.1 mL of the spray. Nascobal Nasal Spray is provided in a carton containing a nasal spray actuator with dust cover, a bottle of nasal spray solution, and a package insert. One bottle will deliver 50 doses (NDC 3065-7725-00).

PHARMACIST ASSEMBLY INSTRUCTIONS FOR NASCOBAL NASAL SPRAY

The pharmacist should assemble the Nascobal Nasal Spray unit prior to dispensing to the patient, according to the following instructions:

1. Open the carton and remove the spray actuator and spray solution bottle.
2. Assemble Nascobal Nasal Spray by unscrewing the white cap from the spray solution bottle and screwing the actuator unit tightly onto the bottle. Make sure the clear dust cover is on the pump unit.
3. Return the nasal spray carton to the pharmacist for disposal.

INFORMATION FOR PATIENTS

Patients with pernicious anemia should be instructed that they will require weekly intranasal administration of Nascobal Nasal Spray for the remainder of their lives. Failure to do so will result in the anemia and in development of inapthacizing 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 B12, 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 Nasal Spray at least one hour before or one hour after ingestion of hot foods or liquids.

Patients with pernicious anemia should be advised to take Nascobal Nasal Spray weekly. The need for vitamin B12 is increased by pregnancy and lactation.

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

LABORATORY TESTS

Persons taking most antibiotics, methotrexate or pyrimethamine should not receive vitamin B12, because these drugs cause folic acid deficiency.

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 B12 is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this is believed to be related to underlying pathology and not to treatment with vitamin B12.

PREGNANCY

Pregnancy Category C: Animal reproduction studies have not been conducted with vitamin B12. It is also not known whether vitamin B12 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 B12 is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B12 that are recommended by the Food and Nutrition Board, National Academy of Science - National Research Council for pregnant women should be consumed during pregnancy.

NURSING MOTHERS

Vitamin B12 appears in the milk of nursing mothers in concentrations which approximate the mother’s vitamin B12 blood level. Amounts of vitamin B12 consumed during lactation.

EDUCATION

Instruct patients on the correct use of Nascobal Nasal Spray. Patients should understand the importance of completing the prescribed therapy. Failure to do so will result in the anemia and in development of inapthacizing and irreversible damage to the nerves of the spinal cord. Also, patients should be advised to take folic acid in place of vitamin B12, because the former may prevent anemia but allow progression of subacute combined degeneration of the spinal cord.

NASCOBAL NASAL SPRAY

Mistakes and errors in pituitary anatomy: 6.5% 7.9% 7.9%

NASCOBAL NASAL SPRAY

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NASCOBAL NASAL SPRAY

Mistakes and errors in pituitary anatomy: 6.5% 7.9% 7.9%
nascobal® nasal spray
(Cyanocobalamin, USP)
500 mcg/spray
2.3 mL (8 sprays)
FOR NASAL USE ONLY

Manufactured for:
Questcor Pharmaceuticals, Inc.
Union City, CA 94587 USA

Each 0.1 mL contains 500 mcg Cyanocobalamin USP and the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

One bottle will deliver eight doses.

Read instructions carefully before using.
See package insert for complete prescribing information.

PATIENT INSTRUCTIONS
Take medication as directed by your physician. For proper use of the spray actuator, read the following instructions carefully.

1. Blow nose gently to clear both nostrils.
2. Remove cover. The very first time Nascobal® Nasal Spray is used, prime the pump by placing nozzle between first and second finger with thumbs on the bottom of bottle. Pump unit firmly and quickly until first appearance of spray. Then prime actuator an additional 3 times (Fig. 1). The pump is now ready for use.
3. Insert tip approximately 1/2” into one nostril, pointing the tip toward the back of the nose. Close other nostril with your forefinger and tilt head slightly forward.
4. Pump unit firmly and quickly by pushing down on the "finger grips" of the pump unit and against the thumb at the bottom of the bottle. Sniff gently with your mouth closed (Fig. 2).
5. After dosing, remove pump-unit from nose. Wipe nozzle with a clean tissue after use. Replace clear cover on pump unit. When not in use, store pump unit upright in carton. Replace once before each use.
6. Discard the bottle after the 8th dose. The best way to safely dispose of the unit is to unscrew the cap, rinse the bottle and pump assembly under a water faucet, and dispose of the parts in a waste can or any container inaccessible to children.

Rx Only
NDC 63004-7733-5

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Proof Approved By:
DATE:
Submit Revised Proof:

NOTE:
Proof colors do not represent exact PMS colors. Please check current PMS guide.

Phone (201) 768-1900 • Fax (201) 768-4627
E-Mail address: norwood@thecontrolgroup.net
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**Proof Approval Form**

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**Proof Dates**
- 9/2/04
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- 9/16/04

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**Nascobal Nasal Spray**

NDC 63004-7733-5
FOR NASAL USE ONLY

(Cyanocobalamin, USP)
500 mcg/spray
2.3 mL (8 sprays)

For use in ONE nostril
unless otherwise directed
by your physician.

Questcor Pharmaceuticals, Inc.
Union City, CA 94587, USA
Lot No. XXXXX

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350% enlarged

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**NASTECH: QUESTCOR: Nascobal Nasal Spray**

Customer:

P.O. No.:

Job number: NAS8

Size: J 3/8 x 2 7/8

Comments: UPC Code human readable: N3 63004-77335 7

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Reviewed by: Date

Submit Revised Proof: Date

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Phone (201) 784-8721 • Fax (201) 784-1527
E-Mail address: control@thecontrolgroup.net

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