Treat $B_{12}$ deficiency.

Sustain serum $B_{12}$ levels.

**Nascobal**

The nasal spray that sustains serum $B_{12}$ levels.

*Nascobal (Cyanocobalamin, USP) Nasal Spray* is contraindicated in patients with sensitivity to cobalt and/or vitamin $B_{12}$ or any component of the medication.

Please see Indication and Important Safety Information on back cover and complete enclosed Prescribing Information.
In a 4-week crossover clinical study,

Patients taking Nascobal® maintained therapeutic serum levels²

- Rapid absorption: peak serum levels achieved 1 to 2 hours postdose²
- Higher therapeutic levels: once-a-week Nascobal maintained higher serum B₁₂ levels than 1 IM B₁₂ injection after 28 days²
- Sustained levels: therapeutic serum B₁₂ levels maintained in Nascobal patients²

Patients treated with Nascobal should understand the importance of returning for follow-up blood tests every 3 to 6 months to confirm adequacy of therapy.

In a crossover study of 25 patients with a history of B₁₂ malabsorption, single-dose cyanocobalamin 100-mcg IM injection was given and monitored for 28 days, followed by 4 weekly doses of Nascobal 500 mcg/0.1 mL. One patient withdrew from study prior to receiving Nascobal.
The B₁₂ treatment with the convenience of a nasal spray.

Nascobal® offers:

- Patient-administered dosing
- No association with pain of injection
- Tasteless and odorless fine mist
- Easily portable—for the on-the-go patient

Incidence of possibly related adverse events in a comparative clinical trial¹

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Nascobal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4%</td>
</tr>
</tbody>
</table>

N=24

Please see Indication and Important Safety Information on back cover and enclosed complete Prescribing Information.
Nascobal is a registered trademark of Par Pharmaceutical, Inc.

The nasal spray that sustains serum B12 levels.¹,²

Widely available on managed care formularies

• Nearly 90% of patients with commercial insurance are covered.

• Less than 1% of commercially insured patients require a prior authorization.

INDICATION
Nascobal (Cyanocobalamin, USP) Nasal Spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B12 therapy and who have no nervous system involvement.

Nascobal Nasal Spray is also indicated for the treatment of some vitamin B12 deficiencies including dietary deficiency of vitamin B12 occurring in strict vegetarian diets; malabsorption of vitamin B12 resulting from conditions including HIV infection, AIDS, Crohn's disease; inadequate secretion of intrinsic factor resulting from conditions including gastric atrophy; and subtotal gastrectomy; total gastrectomy; competition for vitamin B12 by intestinal parasites or bacteria; and inadequate utilization of vitamin B12 that may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.

IMPORTANT SAFETY INFORMATION
Nascobal (Cyanocobalamin, USP) Nasal Spray is contraindicated in patients with sensitivity to cobalt and/or vitamin B12 or any component of the medication. If a patient is not properly maintained with Nascobal Nasal Spray, intramuscular vitamin B12 is necessary. Vitamin B12 concentrations must be monitored.

Patients with pernicious anemia should be instructed that they will require weekly administration of Nascobal Nasal Spray 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. Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy. Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B12 may unmask this condition. Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12.

Side effects thought to be related to Nascobal use are usually mild and include headache, nausea, and rhinitis.

See complete Prescribing Information enclosed.


For more information, you and your patients can visit our Web site at www.nascobal.com
Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B12 may unmask this condition.

Vitamin B12 is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B12 should be avoided. As with all medications, it should be used only as directed. Failure to follow medical advice may mask the true diagnosis.

PRECAUTIONS

I. General

A. Significant and/or fatal effects of vitamin B12 deficiency have been reported in patients treated with chloramphenicol, and folic acid or folate. Such effects may be due to the competitive inhibition of vitamin B12 absorption by chloramphenicol, and folic acid or folate.

B. Vitamin B12 deficiency that is allowed to progress for longer than three months may produce permanent degenerative changes in the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B12 deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result.

C. Vitamin B12 deficiency that is allowed to progress for longer than three months may produce permanent degenerative changes in the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B12 deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result.

D. Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B12 therapy.

E. Vitamin B12 deficiency that is allowed to progress for longer than three months may produce permanent degenerative changes in the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B12 deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result.

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G. Patients with early Leber’s disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.

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Y. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result.

Z. Patients with early Leber’s disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.

\[ \text{Figure. Vitamin B12 Serum Trough Levels After Intramuscular Solution (IM) of 100 mcg and Nasal Gel (IN) Administration of 500 mcg Cyanocobalamin After Weekly Doses.} \]
If the patient is not properly maintained with Nascobal® Nasal Spray, intramuscular vitamin B12 is necessary for adequate treatment of the patient. This should be a reminder to all patients, and the efficacy of the patient observed in follow up for the first time on a daily regimen.

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

2. INFORMATION FOR PATIENTS

Patients with pernicious anemia should be instructed that they will require weekly intramuscular administration of Nascobal Nasal Spray for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incipient and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking too acid or placebo of vitamin B12, because the former may cause 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.)

A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B12. Therefore, patients following such a diet should be advised to take Nascobal Nasal Spray weekly. The need for vitamin B12 is increased by pregnancy and lactation. Deficiency has been recognized in infants whose mothers were breast fed, even though the mothers had no symptoms of deficiency at the time.

Because the nasal dosage forms of Vitamin B12 have a lower absorption than intramuscular dosage, nasal dosage forms are administered weekly, rather than the monthly intramuscular dosage. As shown in the Figure above, at the end of a month, weekly nasal administration results in significantly higher serum Vitamin B12 levels than after intramuscular administration. The patient should also understand the importance of return for follow-up blood tests every 3 to 6 months to confirm adequacy of the therapy.

Careful instructions on the actuator assembly, removal of the safety clip, priming of the actuator and nasal administration of Nascobal Nasal Spray 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 B12, folate and iron levels should be obtained prior to treatment . Folate levels are low, folate should also be administered. All hematologic parameters should be normal when beginning treatment with Nascobal® Nasal Spray. Vitamin B12, folate and peripheral blood counts must be monitored initially at one month after the start of treatment with Nascobal® Nasal Spray, and then at intervals of 3 to 6 months.

A decline in the serum levels of B12 after one month of treatment with B12 nasal spray 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 B12 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 following such a diet should be advised to take Nascobal Nasal Spray weekly. The need for vitamin B12 is increased by pregnancy and lactation. Deficiency has been recognized in infants of breast fed, even though the mothers had no symptoms of deficiency at the time.

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See LABORATORY TESTS for monitoring B12 levels and adjustment of dosage.

4. DRUG/LABORATORY TEST INTERACTIONS

Persons taking methotrexate, methylene blue or pyrimethamine may excrete folic acid and vitamin B12 diagnostic blood assays.

Coughs, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce maldistribution of vitamin B12.

5. CARDIODYNAMICS, MATRACHIASIS, 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, in therapeutic doses, 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 B12.

6. 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.

7. NURSING MOTHERS

Vitamin B12 is excreted in the milk of nursing mothers in concentrations which approximate the mother's vitamin B12 blood level. Amounts of vitamin B12 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

Information on 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 B12 deficient patients in hemorrhagic or anemia (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B12 were generally mild. One patient reported severe headache following intramuscular dosing. Similarly, a few adverse experiences of moderate intensity were reported following intranasal dosing (two headaches and rhinitis, one skin rash, one generalized pruritus, one generalized pain, and one generalized rash).

The incidence of 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 judged as “certain” or “probable”. Of the adverse experiences judged as “probable” relationship to the study drug, anemia, reactions, intranasal, and rhinitis were reported following dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration.

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

- Anaphylactic shock and death (See Warnings and Precautions).
- Cardiogenic: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.
- Hematologic: Thrombocytopenia, anemia, aplastic anemia.
- Gastrointestinal: Mild/moderate diarrhea.
- Dermatologic: Itching; transitory exanthema.
- Miscellaneous: Peeling of scolding of the entire body.

OVERDOSE

No overdosage has been reported with Nascobal Nasal Spray, Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration or parental vitamin B12.

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

Before the first dose and administration, the pump must be primed. Remove the plastic cover and the plastic safety dip from the pump. To prime the pump, place nozzle 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 reprimed before each dose. Prime the pump once immediately before each administration of dose 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 bottle containing 1.3 mL of solution. It is available in a dosage strength of 500 mcg per spray (approximately 0.1 mL spray per application). Each actuator is provided. This actuator, following priming, will deliver 0.1 mL of the solution. Nascobal Nasal Spray is supplied in a carton containing a nasal spray actuator with dust cover, a bottle of nasal spray solution, and a package insert. Each carton may contain (B20) 66646-070-80.

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 first unscrewing the white cap from the spray solution bottle and screwing the actuator unit tightly onto the bottle.

3. Return the Nascobal Nasal Spray bottle to the carton for dispensing to the patient.

INFORMATION FOR PATIENTS

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At a few adverse experiences of moderate intensity were reported following intramuscular dosing (two headaches and rhinitis; one dyspepsia, and one skin rash). The patient should also understand the importance of

Careful instructions on the actuator assembly, removal of safety clip, priming of the actuator and nasal administration of Nascobal Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient.

STORAGE CONDITIONS

Protect from light. Keep covered in carton until ready to use. Store upright at controlled room temperature 10°C to 30°C (50°F to 86°F). Protect from freezing.

To report suspected adverse reactions, contact Par Pharmaceutical Companies, Inc. at 1-800-828-9393.