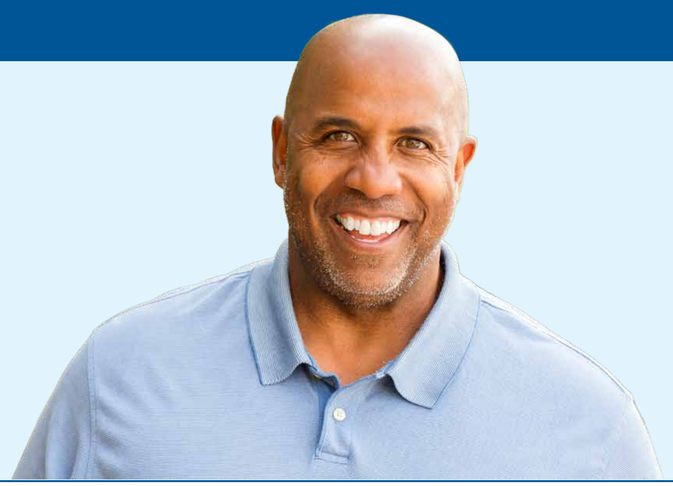
Endocrinologists

IDENTIFYING PATIENTS **WITH VITAMIN B_{12} DEFICIENCY**



WILLIAM, 48 YEARS OLD

- Divorced, with 2 children
- Marketing Director
- 6 ft 0 in, 243 lb
- BMI: 33 (obese)
- BP: 148/90
- Commercial insurance

HISTORY
Diagnosed with Type 2 diabetes 6 years ago
Hypercholesterolemia
Hypertensive
Gastroesophageal reflux disease (GERD)

MEDICATIONS	
Metformin	Pantoprazole
Atorvastatin	Beta-blocker
Hydrochlorothiazide	

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY

NASCOBAL® is contraindicated in patients with sensitivity to cobalt, vitamin B_{12}, or any component of the medication. Anaphylactic shock and death have been reported with parenteral forms of vitamin B_{12}. Consider administering an intradermal test dose of parenteral vitamin B_{12} to patients suspected of cyanocobalamin hypersensitivity prior to starting NASCOBAL®.

INDICATIONS

- Vitamin B_{12} maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B_{12} deficiency not due to pernicious anemia
- Prevention of vitamin B_{12} deficiency in adult patients with vitamin B_{12} requirements in excess of normal

Please see additional Important Safety Information throughout.
Please see the full Prescribing Information available from representative.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

RATIONALE FOR TESTING AND TREATING VITAMIN B_{12} DEFICIENCY

IN DIABETICS TAKING METFORMIN

Vitamin B_{12} deficiency is a potential comorbidity of Type 2 diabetes.[1] Despite its ability to effectively lower blood glucose in patients with Type 2 diabetes, metformin has been documented to decrease vitamin B_{12} levels. Risk of metformin-associated vitamin B_{12} deficiency in patients with Type 2 diabetes increases with increasing age, higher metformin dose, and longer duration of use.[2]

Reports indicate that 30% of patients receiving long-term metformin treatment experience malabsorption of vitamin B_{12}, with reductions in serum vitamin B_{12} concentration of 14% to 30%.[3]

Sensory polyneuropathy could be a symptom of vitamin B_{12} deficiency that closely mimics diabetic neuropathy. This underscores the need to check vitamin B_{12} levels and screen these patients for vitamin B_{12} deficiency.[2]

SPECIMEN: SERUM (HYPOTHETICAL)

Test Name	Patient's Results	Ref. Range	Units
Vitamin B_{12}	L190	200-1000[4]	pg/mL
Folate (RBC)	L320	340-1020[4]	ng/mL
MMA - Methylmalonic Acid	H0.425	>0.376[4]*	µmol/L
Homocysteine	H13.7	>13.2[4]*	µmol/L

*Critical Range L = Abnormal Low H = Abnormal High

NASCOBAL® may be considered as a vitamin B_{12} supplement in circumstances where a prescriber has determined that metformin should be continued in a diabetic patient where vitamin B_{12} deficiency persists.

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY (cont)

Patients with Leber's disease who were treated with vitamin B_{12} suffered severe and swift optic atrophy. NASCOBAL® is not recommended for use in patients with Leber's optic atrophy.

Doses of vitamin B_{12} exceeding 10 mcg daily may produce hematologic response in patients with folate-deficient megaloblastic anemia, and may therefore mask a previously unrecognized folate deficiency. NASCOBAL® is not a substitute for folic acid. Assess both vitamin B_{12} and folate levels prior to initiating therapy with NASCOBAL®.

Hypokalemia, thrombocytosis and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}.
Serum potassium levels and platelet count should be monitored.

Please see additional Important Safety Information throughout.
Please see the full Prescribing Information available from representative.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

THE ONLY FDA-APPROVED PRESCRIPTION VITAMIN B_{12} NASAL SPRAY[5]

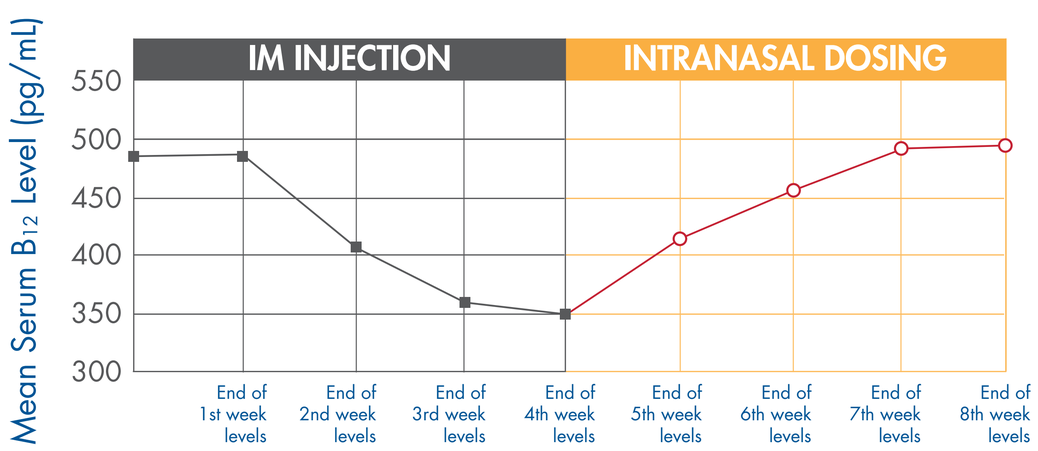
CLINICALLY PROVEN TO HAVE INCREASED VITAMIN B_{12} LEVELS FROM THE FIRST DOSE[6]

- Achieved mean peak serum vitamin B_{12} concentration within 1.5 hours[6]*
- Reached mean peak concentration of 1,021 pg/mL[6]*
- At 72 hours, mean serum vitamin B_{12} level was increased by 46% above baseline[6]*

*In 21 healthy volunteers under fasting conditions, a single 500-mcg dose of NASCOBAL® was given and monitored for 3 days. Data are based on baseline-uncorrected serum vitamin B_{12} levels.[6]

INTRANASAL ADMINISTRATION HAS MAINTAINED HEALTHY VITAMIN B_{12} LEVELS

Serum vitamin B_{12} levels in patients with pernicious anemia[7]



- Once-a-week Intranasal Dosing maintained higher serum vitamin B_{12} levels than 1 intramuscular vitamin B_{12} injection after 28 days

In 24 patients with a history of pernicious anemia, a single-dose cyanocobalamin 100-mcg/mL IM injection was given and monitored for 28 days, followed by 4 once-weekly doses of intranasal (IN) vitamin B_{12} gel 500 mcg/0.1 mL. Mean baseline serum vitamin B_{12} prior to IN dosing = 351.4 pg/mL, and at day 28 = 480.7 pg/mL.[7]

In a separate study, bioavailability of vitamin B_{12} nasal spray was 10% less than vitamin B_{12} nasal gel. Clinical significance is unknown.[8]

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY (cont)

Treatment with vitamin B_{12} may unmask signs of polycythemia vera. Patients exhibiting clinical or hematologic response consistent with polycythemia vera should be referred for further evaluation.

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. Consider the potential for concomitant drugs to interfere with vitamin B_{12} and folate diagnostic blood assays. Vitamin B_{12} and peripheral blood counts must be monitored initially at one month after the start of treatment, and then at intervals of 3 to 6 months. If a patient is not properly maintained with NASCOBAL®, consider alternative therapy.

Please see additional Important Safety Information throughout.
Please see the full Prescribing Information available from representative.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

CONVENIENT,
ONCE-WEEKLY DOSING REGIMEN

SELF-ADMINISTERED: 1 SPRAY, 1 NOSTRIL, 1x A WEEK[8]

NASCOBAL® Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids.

Dose adjustments may be required.

AN AFFORDABLE TREATMENT
FOR VITAMIN B_{12} DEFICIENCY

ELIGIBLE PATIENTS MAY GET NASCOBAL® FOR AS LITTLE AS $0 PER MONTH*

Download Copay Cards at Nascobal.com.

*Patients may redeem this offer ONLY when accompanied by a valid prescription. Offer is valid up to a maximum benefit of $150. Offer is not valid for patients whose prescriptions are reimbursed in whole or in part under Medicaid, Medicare, Medigap, VA, DoD, TRICARE, or any other federal or state programs (such as medical assistance programs) or where otherwise prohibited by law. Offer is not valid in VT or where prohibited in whole or in part. This offer may be amended or ended at any time without notice.

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY (cont)

If NASCOBAL® is used concomitantly with chloramphenicol, monitor for reduced efficacy and, if needed, consider an alternative therapy.

The limited available data on NASCOBAL® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

The most common adverse reactions (≥4%) were infection, headache, glossitis, paresthesia, asthenia, nausea and rhinitis.

Please see additional Important Safety Information throughout.
Please see the full Prescribing Information available from representative.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

IMPORTANT SAFETY INFORMATION

INDICATIONS

- Vitamin B_{12} maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B_{12} deficiency not due to pernicious anemia
- Prevention of vitamin B_{12} deficiency in adult patients with vitamin B_{12} requirements in excess of normal

Limitations of Use

- NASCOBAL® should not be used for the vitamin B_{12} absorption test (Schilling test).
- In patients with correctible or temporary causes of vitamin B_{12} deficiency, the benefit of continued long-term use of NASCOBAL® following adequate correction of vitamin B_{12} deficiency and underlying disease has not been established.
- The effectiveness of NASCOBAL® in patients with active symptoms of nasal congestion, allergic rhinitis or upper respiratory infection has not been determined. Treatment with NASCOBAL® should be deferred until symptoms have subsided.

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY

NASCOBAL® is contraindicated in patients with sensitivity to cobalt, vitamin B_{12}, or any component of the medication. Anaphylactic shock and death have been reported with parenteral forms of vitamin B_{12}. Consider administering an intradermal test dose of parenteral vitamin B_{12} to patients suspected of cyanocobalamin hypersensitivity prior to starting NASCOBAL®.

Patients with Leber's disease who were treated with vitamin B_{12} suffered severe and swift optic atrophy. NASCOBAL® is not recommended for use in patients with Leber's optic atrophy.

Doses of vitamin B_{12} exceeding 10 mcg daily may produce hematologic response in patients with folate-deficient megaloblastic anemia, and may therefore mask a previously unrecognized folate deficiency. NASCOBAL® is not a substitute for folic acid. Assess both vitamin B_{12} and folate levels prior to initiating therapy with NASCOBAL®.

Hypokalemia, thrombocytosis and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Serum potassium levels and platelet count should be monitored.

Treatment with vitamin B_{12} may unmask signs of polycythemia vera. Patients exhibiting clinical or hematologic response consistent with polycythemia vera should be referred for further evaluation.

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. Consider the potential for concomitant drugs to interfere with vitamin B_{12} and folate diagnostic blood assays. Vitamin B_{12} and peripheral blood counts must be monitored initially at one month after the start of treatment, and then at intervals of 3 to 6 months. If a patient is not properly maintained with NASCOBAL®, consider alternative therapy.

If NASCOBAL® is used concomitantly with chloramphenicol, monitor for reduced efficacy and, if needed, consider an alternative therapy.

The limited available data on NASCOBAL® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

The most common adverse reactions (≥4%) were infection, headache, glossitis, paresthesia, asthenia, nausea and rhinitis.

Please see the full Prescribing Information available from representative.

References: 1. Pflipsen M, Oh R, Saguil A, et al. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes: A cross-sectional study. *J Am Board Fam Med*. 2009;22:528–534. **2.** Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? *J Diabetes Metab Disord*. 2013;12(1):17. **3.** Liu Q, Li S, Quan H, Li J. Vitamin B12 status in metformin treated patients: systematic review. *PLoS ONE*. 2014;9(6):e100379. **4.** Parrott J, Frank L, Rabena R, et al. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. *Surg Obes Relat Dis*. 2017:1-15. **5.** US Food and Drug Administration. Approved drug products with therapeutic equivalence evaluations. 41st ed. https://www.fda.gov/media/71474/download. Accessed January 28, 2021. **6.** Data on File. DOF-NS-02. Endo Pharmaceuticals Inc.; 2016. **7.** Data on File. DOF-NS-01. Endo Pharmaceuticals Inc.; 2015. **8.** NASCOBAL® [Prescribing Information]. Chestnut Ridge, NY: Par Pharmaceutical Companies.

NASCOBAL® (Cyanocobalamin, USP) Nasal Spray

endo pharmaceuticals
an endo international company

NS-05581/January 2021 www.nascobal.com 1-800-462-ENDO (3636)