CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021642Orig1s020

Trade Name: **Nascobal Nasal Spray**

Generic Name: **cyanocobalamin**

Sponsor: **Par Pharmaceutical Inc.**

Approval Date: 06/06/2014

Indications: Nascobal 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 as a supplement for other vitamin B12 deficiencies.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021642Orig1s020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021642/S-020

SUPPLEMENT APPROVAL

Par Pharmaceutical Inc.
Attention: Meredith Selby
Director, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Selby:

Please refer to your Supplemental New Drug Application (sNDA) dated March 11, 2013, received March 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nascobal (cyanocobalamin) nasal spray.

We acknowledge receipt of your amendments dated June 28, October 25, November 14, and December 9, 2013, and February 20 and April 25, 2014.

The October 25, 2013, submission constituted a complete response to our July 12, 2013, action letter.

This "Prior Approval" supplemental new drug application proposes a new unit dose device to replace the current packaging configuration of 1.3 mL fill volume in 3-mL multi-dose glass bottles.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert) submitted on April 25, 2014, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on October 25, 2013, and April 25, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021642/S-020**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES: Package Insert, Carton and Immediate Container Labels for Nascobal (cyanocobalamin) nasal spray

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021642Orig1s020

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021642/S-020

COMPLETE RESPONSE

Par Pharmaceuticals, Inc.
Attention: Meredith Selby
Director, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Selby:

Please refer to your Supplemental New Drug Application (sNDA) dated March 11, 2013, received March 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nascobal (cyanocobalamin) Nasal Spray, 500 mcg/spray.

We acknowledge receipt of your amendment dated June 28, 2013.

This supplemental new drug application proposes the supply of Nascobal Nasal Spray in a new unit-dose device to replace the current packaging configuration of 1.3 mL in 3 mL multi-dose glass bottles.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Your justification provided to explain the failure of bioequivalence (BE) for the upper bound of the 90% CI for AUC$_{(0-t)}$ for the baseline-corrected cyanocobalamin data is not acceptable. Based on the review of the baseline cyanocobalamin data provided for the 24 hours prior to the administration of the dose, the levels of endogenous cyanocobalamin do not have very high variability. To support and justify the failure of BE for the corrected data, we recommend that you provide data to support the inherent variability of endogenous cyanocobalamin; e.g., basal cyanocobalamin levels for a minimum period of 72 hours.

2. Clarify if any degradation products from benzalkonium chloride were observed during the inverted accelerated stability studies [redacted] (b) (4) .

LABELING

3. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology 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/

JAMES P SMITH
07/12/2013
on behalf of Mary Parks

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

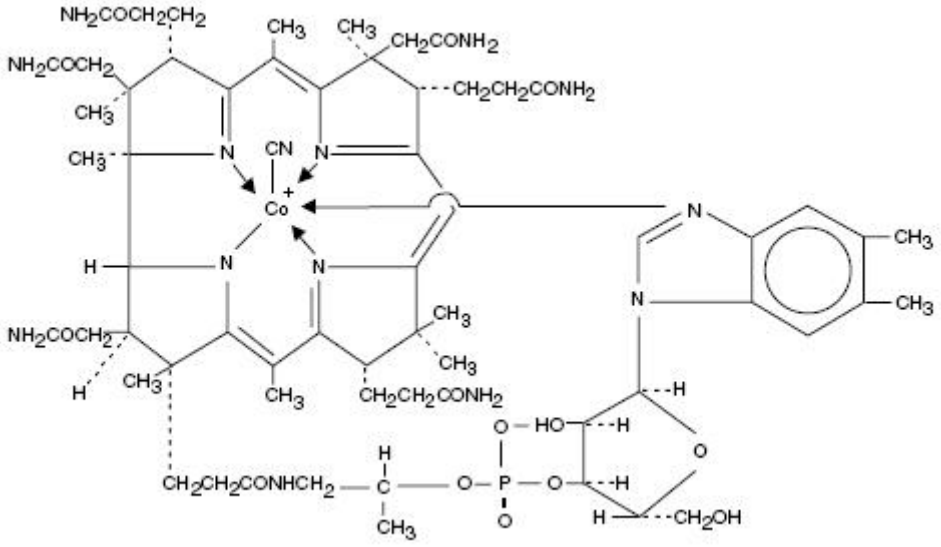
021642Orig1s020

LABELING

Nascobal®
(Cyanocobalamin, USP)
Nasal Spray
500 mcg/spray
0.125 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® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B_{12}) for administration as a spray to the nasal mucosa. Each unit dose device of Nascobal Nasal Spray contains 0.125 mL of a 500 mcg/0.1mL solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water. The spray solution has a pH between 4.5 and 5.5. Each spray delivers an average of 500 mcg of cyanocobalamin.

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-methyltetrahydrofolate, 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

A three way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B_{12} nasal spray to the B_{12} nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared 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 B_{12} obtained after baseline correction following administration of intranasal spray was 757.96 +/- 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 B_{12} nasal spray was found to be 10% less than the B_{12} nasal gel. The 90% confidence intervals for the $\log_e$-transformed $AUC_{(0\text{-}t)}$ and C_{max} was 71.71% - 114.19% and 71.6% - 118.66% respectively.

In pernicious anemia patients, once weekly intranasal dosing with 500 mcg B_{12} gel 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.

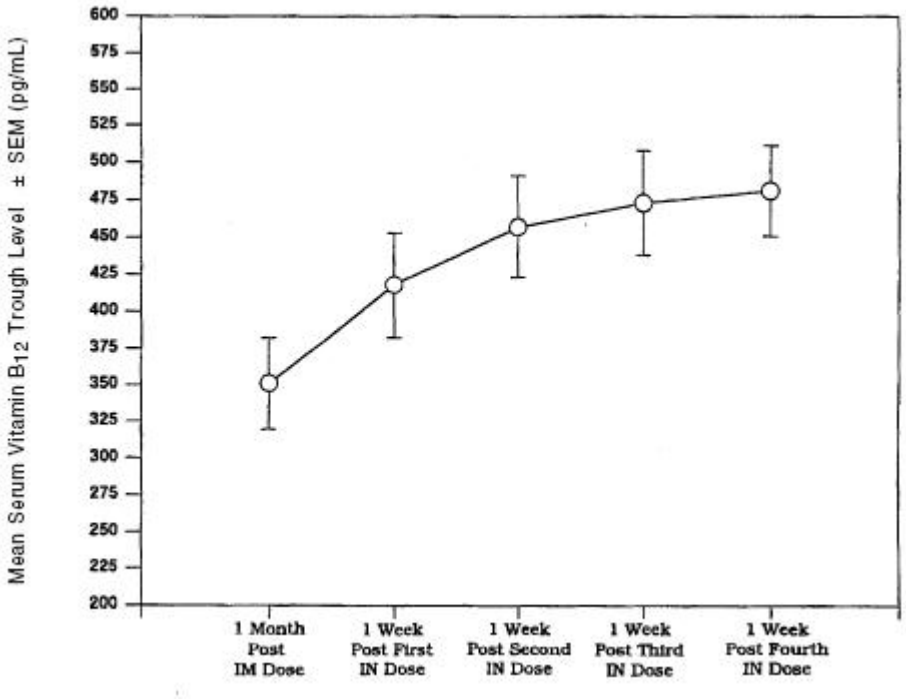


Figure. Vitamin B_{12} Serum Trough Levels After Intramuscular Solution (IM) of 100 mcg and Nasal Gel (IN) Administration of 500 mcg Cyanocobalamin After Weekly Doses.

INDICATIONS AND USAGE

Nascobal Nasal Spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement.

Nascobal Nasal Spray is also indicated as a supplement for other vitamin B_{12} deficiencies, including:

I. Dietary deficiency of vitamin B12 occurring in strict vegetarians (Isolated vitamin B_{12} deficiency is very rare).

II. 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.

III. 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.

IV. 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.

V. 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 of a gluten-free diet in non-tropical 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 Nasal Spray is not suitable for vitamin B_{12} absorption test (Schilling Test).

CONTRAINDICATIONS

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 Nasal Spray or Nascobal Nasal Gel.

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.

PRECAUTIONS

1. GENERAL

An intradermal test dose of parenteral vitamin B_{12} is recommended before Nascobal Nasal Spray 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® Nasal Spray, 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 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.

2. 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® Nasal Spray.

Vitamin B_{12} blood levels 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 B_{12} after one month of treatment with B_{12} 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 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.

3. 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}.

4. 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}.

5. 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.

6. 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.

7. 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). In the pharmacokinetic study comparing Nascobal Nasal Spray and Nascobal Nasal Gel, the incidence of adverse events was similar.

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 Nasal Spray, Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration or parenteral vitamin B_{12}.

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 B_{12} levels should be obtained to establish adequacy of therapy.

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

HOW SUPPLIED

Nascobal Nasal Spray, 500 mcg is supplied in boxes of 4 unit dose nasal spray devices and a package insert (NDC 49884-270-82). Each unit dose spray delivers 500 mcg of cyanocobalamin, USP.

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 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 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 B_{12}. Therefore, patients following such a diet should be advised to take Nascobal Nasal Spray 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.

Because the nasal dosage forms of Vitamin B_{12} 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 B_{12} levels than after intramuscular administration. 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.

STORAGE CONDITIONS

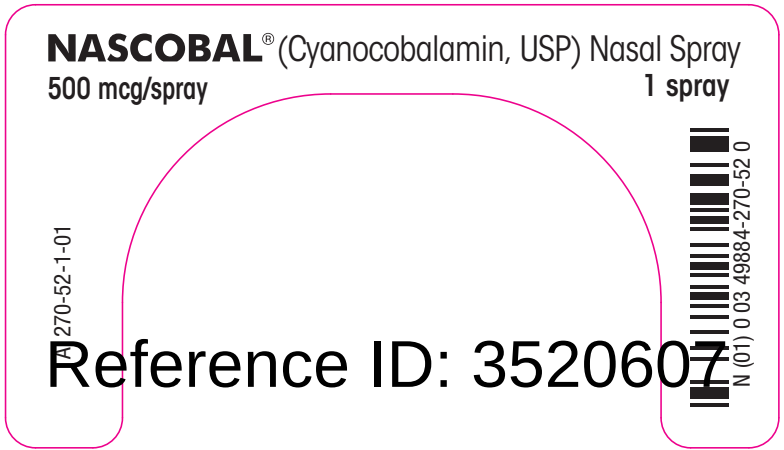
Protect from light. Keep covered in carton until ready to use. Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.

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

Distributed by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

OS270-01-1-05
Rev. 04/14

side a



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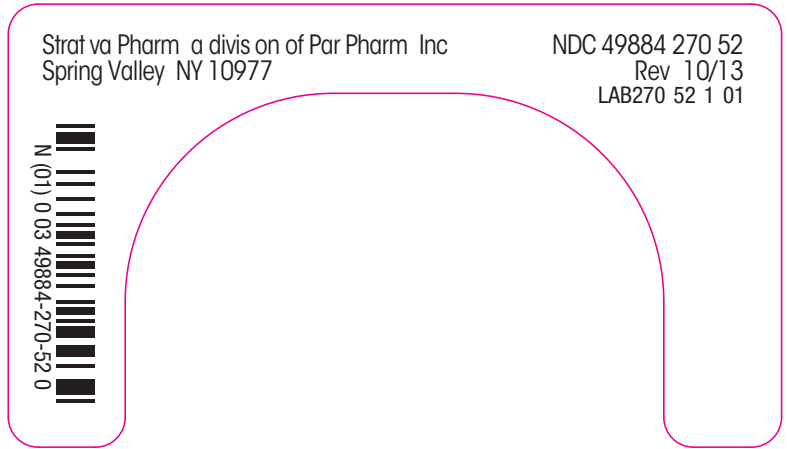

Peel off

Rev. 10/2013 NDC 49884-270-52

NASCOBAL®

(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

FOR NASAL USE ONLY

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP.

1 SPRAY/DEVICE. DO NOT PRIME BEFORE USE.

See package insert for full Prescribing Information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only.

SAMPLE USE ONLY
NOT FOR RESALE

Distributed by:
Strativa Pharmaceuticals,
a division of Par Pharmaceutical, Inc.
Spring Valley, NY 10977

BL270-52-1-01

N (01) 1 03 49884-270-52 7

Reference ID: 3520607

NDC 49884-270-52 Rev. 10/2013

Peel off

NASCOBAL®

(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

FOR NASAL USE ONLY

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP.

1 SPRAY/DEVICE. DO NOT PRIME BEFORE USE.

See package insert for full Prescribing Information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only.

SAMPLE USE ONLY
NOT FOR RESALE

Distributed by:
Strativa Pharmaceuticals,
a division of Par Pharmaceutical, Inc.
Spring Valley, NY 10977

BL270-52-1-01

N (01) 1 03 49884-270-52 7

Peel off

Rev. 10/2013 NDC 49884-270-52

NASCOBAL®

(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

FOR NASAL USE ONLY

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP.

1 SPRAY/DEVICE. DO NOT PRIME BEFORE USE.

See package insert for full Prescribing Information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only.

Distributed by:
Strativa Pharmaceuticals,
a division of Par Pharmaceutical, Inc.
Spring Valley, NY 10977

BL270-23-1-01

N (01) 1 03 49884-270-52 7

Reference ID: 3520607

NDC 49884-270-52 Rev. 10/2013

Peel off

NASCOBAL®

(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

FOR NASAL USE ONLY

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP.

1 SPRAY/DEVICE. DO NOT PRIME BEFORE USE.

See package insert for full Prescribing Information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only.

Distributed by:
Strativa Pharmaceuticals,
a division of Par Pharmaceutical, Inc.
Spring Valley, NY 10977

BL270-23-1-01

N (01) 1 03 49884-270-52 7

Rx Only NDC 49884-270-52

NASCOBAL®

(Cyanocobalamin, USP) Nasal Spray 500 mcg/spray

This pack contains: 1 single-use nasal spray device. One spray per device.

This single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP and contains the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

SAMPLE USE ONLY
NOT FOR RESALE

DO NOT PRIME BEFORE USE.
KEEP OUT OF REACH OF CHILDREN.

N 3 49884 - 270-52 0

www.nascobal.com

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

See package insert for full Prescribing Information. Store at controlled room temperature 15°-30°C (59°-86°F).

For nasal use only. Protect from light. Protect from freezing.

Strativa PHARMACEUTICALS

Distributed by:
Strativa Pharmaceuticals, a division of Par Pharmaceutical, Inc.
Spring Valley, NY 10977

NDC 49884-270-52
NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

Rx Only NDC 49884-270-52

PATIENT INSTRUCTIONS

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

1. The unit contains only 1 spray: **DO NOT prime before use.**
2. Blow nose gently to clear both nostrils.
3. Hold the unit with your thumb supporting it at the bottom and your index and middle fingers on either side of the nozzle. (**Figure #1**)
4. Gently close one nostril with your other index finger. Insert the nozzle into open nostril approximately ½ inch, or as far as feels comfortable and tilt your head slightly forward. Do not press the plunger yet. (**Figure #2**)
5. Breathe in gently through your nose, close your mouth, and at the same time press the plunger firmly with your thumb.
6. Remove the nozzle from your nostril. At the same time, keep your head level for 10 to 20 seconds while gently breathing in through your nose and breathing out through your mouth.

Figure #1

Figure #2

www.nascobal.com

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

See package insert for full Prescribing Information. Store at controlled room temperature 15°-30°C (59°-86°F).

For nasal use only. Protect from light. Protect from freezing.

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R04/14 SC270-52-1-02

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

NDC 49884-270-82

Rx Only NDC 49884-270-82

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

This pack contains: 4 single-use nasal spray devices.

One spray per device.

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP and contains the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

DO NOT PRIME BEFORE USE.
KEEP OUT OF REACH OF CHILDREN.

www.nascobal.com

R.04/14
UC270-82-1-02

N 3 49884 - 270 -82 7

PATIENT INSTRUCTIONS

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

1. The unit contains only 1 spray: **DO NOT prime before use.**
2. Blow nose gently to clear both nostrils.
3. Hold the unit with your thumb supporting it at the bottom and your index and middle fingers on either side of the nozzle. (**Figure #1**)
4. Gently close one nostril with your other index finger. Insert the nozzle into open nostril approximately ½ inch, or as far as feels comfortable and tilt your head slightly forward. Do not press the plunger yet. (**Figure #2**)
5. Breathe in gently through your nose, close your mouth, and at the same time press the plunger firmly with your thumb.
6. Remove the nozzle from your nostril. At the same time, keep your head level for 10 to 20 seconds while gently breathing in through your nose and breathing out through your mouth.

Figure #1

Figure #2

Rx Only NDC 49884-270-82

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP and contains the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

One spray per device.

DO NOT PRIME BEFORE USE.
KEEP OUT OF REACH OF CHILDREN.

www.nascobal.com

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

See package insert for full Prescribing Information. Store at controlled room temperature 15°-30°C (59°-86°F).

For nasal use only. Protect from light. Protect from freezing.

Strativa PHARMACEUTICALS
Distributed by:
Strativa Pharmaceuticals,
a division of
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray
500 mcg/spray

NDC 49884-270-82

Rx Only NDC 49884-270-82

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP and contains the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

One spray per device.

DO NOT PRIME BEFORE USE.
KEEP OUT OF REACH OF CHILDREN.

www.nascobal.com

R04/14
OT270-82-1-02

N 3 49884 - 270 -82 7

PATIENT INSTRUCTIONS

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

1. The unit contains only 1 spray: **DO NOT prime before use.**
2. Blow nose gently to clear both nostrils.
3. Hold the unit with your thumb supporting it at the bottom and your index and middle fingers on either side of the nozzle. (**Figure #1**)
4. Gently close one nostril with your other index finger. Insert the nozzle into open nostril approximately ½ inch, or as far as feels comfortable and tilt your head slightly forward. Do not press the plunger yet. (**Figure #2**)
5. Breathe in gently through your nose, close your mouth, and at the same time press the plunger firmly with your thumb.
6. Remove the nozzle from your nostril. At the same time, keep your head level for 10 to 20 seconds while gently breathing in through your nose and breathing out through your mouth.

Figure #1

Figure #2

Rx Only NDC 49884-270-82

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

This pack contains: 4 single-use nasal spray devices.

One spray per device.

Each single-use nasal spray device delivers 500 mcg of Cyanocobalamin, USP and contains the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

DO NOT PRIME BEFORE USE.
KEEP OUT OF REACH OF CHILDREN.

www.nascobal.com

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

500 mcg/spray

See package insert for full Prescribing Information. Store at controlled room temperature 15°-30°C (59°-86°F).

For nasal use only. Protect from light. Protect from freezing.

Strativa PHARMACEUTICALS
Distributed by:
Strativa Pharmaceuticals,
a division of
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

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/s/

JEAN-MARC P GUETTIER
06/06/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

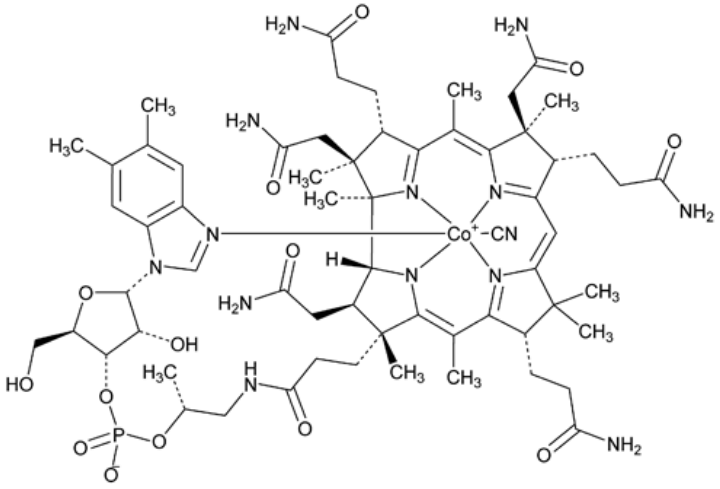
APPLICATION NUMBER:

021642Orig1s020

CHEMISTRY REVIEW(S)

Chemistry Review:# 1	**1. Division:** ONDQA-DMEP	**2. NDA Number:** 21-642
3. Name and Address of Applicant: PAR PHARMACEUTICAL INC One Ram Ridge Road Spring Valley, New York, 10977 United States		**4. Supplement(s):** PAS **Number:** S-020 **Date(s):** 10/25/2013
5. Name of Drug: NASCOBAL® spray, metered		**6. Nonproprietary name:** CYANOCOBALAMIN
7. Supplement Provides for: A new unit dose device		**8. Amendment(s):** 11/14/2013 12/09/2013 02/20/2014
9. Pharmacological Category: Bronchial Asthma	**10. How Dispensed:** R_x	**11. Related Documents:**
12. Dosage Form: Spray, metered pump	**13. Potency:** 500 mcg/spray	

14. Chemical Name and Structure: 5,6-dimethyl-benzimidazolyl cyanocobamide
MF: $C_{63}H_{88}CoN_{14}O_{14}P$; **MW:** 1355.38



15. Comments:

- This supplement provides for Nascobal® Nasal Spray in a unit-dose device and was originally submitted on 03/11/2013.
- This supplement was reviewed by Deepika Arora Lakhani, Ph.D. on 07/10/2013 and recommended for a complete response. The CR letter was sent 07/12/2013 with one biopharmaceutics deficiency and one CMC clarifying comment.
- This supplement was resubmitted on 10/25/2013 and there have been three amendments since that time.
- Sandra Suarez Sharp, Ph.D. found the supplement adequate from a biopharmaceutics perspective on 01/30/2014. An addendum to this review was filed on 04/21/2014 that stated a PMC was not needed.
- Sarah Vee, Pharm.D. found the labeling acceptable on 12/11/2013

16. Conclusion: This supplement is recommended for approval from a CMC perspective

17. Name:	**Signature:**	**Date:**
Erika Englund, Ph.D., Chemist		
18. Concurrence:	**Signature:**	**Date:**
Ramesh Raghavachari, Ph.D., Branch Chief, Br., IX, ONDQA		

Drug Product Information

1. Nascobal® (Cyanocobalamin nasal spray) was approved 01/31/2005 for the maintenance of normal hematologic status in pernicious anemia patients.
2. Cyanocobalamin is a synthetic form of vitamin B_{12}.
3. Nascobal® is a solution of cyanocobalamin, USP administered as a spray to the nasal mucosa. The excipients include sodium citrate, citric acid, glycerin, and benzalkonium chloride in purified water.
4. It is available in 2.3 mL bottles as a metered dose nasal spray (500 mcg/spray).

Chemistry Assessment

NDA21-642 S020 was originally submitted on 03/11/2013 and provided for a new single-dose presentation of Nascobal®. Deepika Arora Lakhani, Ph.D. performed the original review and recommended this supplement for a complete response. One biopharmaceutics deficiency was sent and one CMC clarifying question was sent in the CR letter. The supplement was resubmitted on 10/25/2013. The resubmitted supplement provided for a change to the specification for net content, a response to the biopharmaceutics deficiencies, and a response to the CMC clarifying question regarding possible benzalkonium chloride degradation during stability studies. Sandra Suarez Sharp, Ph.D. reviewed the resubmission of this supplement after the CR and found the supplement adequate from a biopharmaceutics perspective on 01/30/2014 and that a PMC was not required on 04/21/2014. Sarah Vee, Pharm.D. reviewed this supplement on 12/11/2013 and found the labeling acceptable.

(b) (4)

[redacted]

(b) (4)

3.2.P.5.6
The stability studies submitted in support of the original supplement submission showed a faster decrease in the benzalkonium chloride assay when the container was stored inverted rather than upright. The other parameters did not display a similar decrease upon inverted storage. A CMC clarifying comment was sent with the July 12, 2013 Complete Response Letter:

> *Clarify if any degradation products from benzalkonium chloride were observed during the inverted accelerated stability studies* (b) (4),

Par provided a response to this comment in the 10/25/2013 amendment. They proposed that the percentage of Benzalkonium Chloride decreased due to sorption onto the plunger surface. They stated that if the percentage of belzalkonium chloride was decreasing due to decomposition, the decomposition pathway would most likely proceed via an oxidative route. Therefore, the HPLC method was modified to detect more polar degradation products. A short term compatibility study was performed to investigate the interaction of benzalkonium chloride with the plunger material. No significant degradation products were identified, and the most likely cause of the reduction in benzalkonium chloride assay was attributed to sorption on the plunger material. No changes to the specifications were proposed. This is adequate.

Labeling
The package insert was updated with the new presentation size. "Each unit dose device of Nascobal Nasal Spray contains 0.125 mL of a 500 mcg/0.1 mL solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water" was added under description and "Nascobal Nasal Spray, 500 mcg is supplied in boxes of 4 unit dose nasal spray devices and a package insert (NDC 49884-270-82). Each unit dose spray delivers 500 mcg of cyanocobalamin, USP" was added under how supplied. There were no changes to the composition of the drug product. These changes are adequate for the package insert.

Updated container and carton labels were also submitted. The lot number and expiration date are not on the label; however Par provided the following commitment in the 10/25/2013 amendment:

> *Par commits to print the words "Lot:" and "Exp:" online at the same time as we print the numerical information. Due to the small size of the blister label, it is challenging to line up the online printed numbers with the pre-printed text.*

Per FDA request, a net quantity statement of "1 spray" was also added to the labeling in this submission. The list of inactive ingredients were included in the carton label received via e mail on 4/22/2014 and copied below.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

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Overall Evaluation: Adequate

This review covers the resubmitted supplement after the complete response letter. Updated labeling and drug product net content specifications were submitted. In addition, a justification for the decrease in the benzalkonium chloride assay at inverted storage during stability studies was provided. This is adequate and this supplement is recommended for approval from CMC perspective.

Nanotechnology Submission Report Form

Nanotechnology is absent.

Report # (For WG internal use)	
Application and submission number (*e.g.*, I-XXXXXX-P-XXXX)	21-642/S-020

Who has identified the product as a potential for containing nanomaterials? (i.e. Sponsor or CVM)	Nanotechnology not present
Is this a modification of an approved product or another investigational product? If so, what has been modified?	No
Please describe the nanomaterials (*e.g.*, poloxamer 188 micelle with emulsified active, particle size 30 -50 nm, or nanocrystal suspension, particle size 130 – 160 nm, etc.)	None
Does the new formulation have unique properties including effects via engineering of the constituent on the nanoscale? If so, explain.	No
Other information worth recording (*e.g.*, INAD or NADA # of a corresponding product w/o nanomaterials)	No
Reviewer Name, Date, HFV code	Erika Elaine Englund, PhD

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/s/

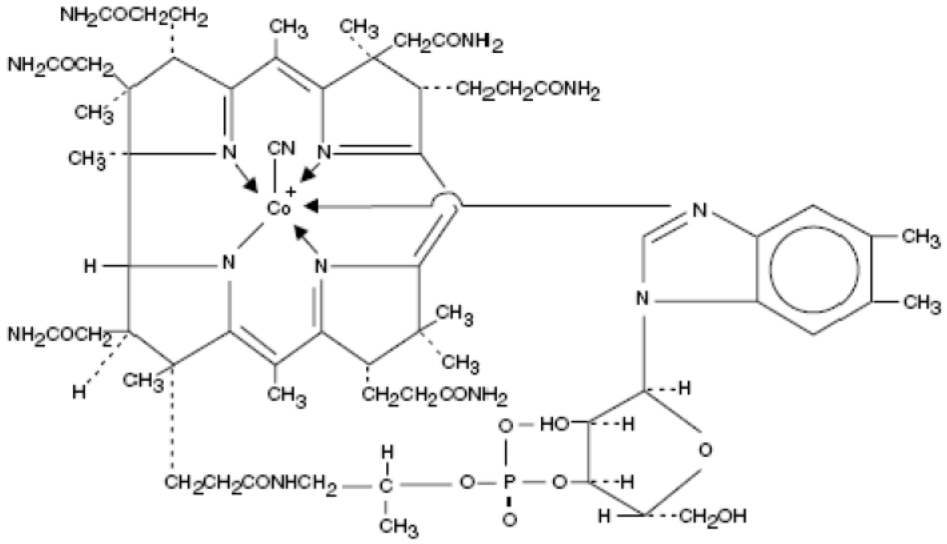
ERIKA E ENGLUND
04/23/2014

RAMESH RAGHAVACHARI
04/23/2014

Chemistry & Biopharmaceutics Review:# 1	**1. Division:** ONDQA/DNDQA/Branch IX	**2. NDA Number: 21-642**
3. Name and Address of Applicant: Par Pharmaceutical, Inc. One Ram Ridge Spring Valley, NY 10977		**4. Supplement(s):** PAS **Number:** S-020 **Date(s):** 12-MAR-2013
5. Name of Drug: Nascobal®		**6. Nonproprietary name:** Cyanocobalamin, USP
7. Supplement Provides for: A new unit dose device.		**8. Amendment(s):**
9. Pharmacological Category: Bronchial Asthma	**10. How Dispensed:** R_x	**11. Related Documents:**
12. Dosage Form: Nasal Spray	**13. Potency:** 500 mcg/spray	

14. Chemical Name and Structure: : (b) (4)

Molecular Formula: $C_{63}H_{88}CoN_{14}O_{14}P$; **MW:** 1355.37 g/mol ; **CAS:** 68-19-9



15. Comments:

- The Applicant is proposing Nascobal® Nasal Spray in a unit-dose device. The unit dose system consists of (b) (4) he device is designed to dispense 100 µL accurately.
- Biopharmaceutics review of the provided in vivo BE study to support equivalence between the proposed unit dose with the approved multi-dose was also conducted by this reviewer.
- From CMC and Biopharmaceutics perspective, COMPLETE RESPONSE is recommended.

16. Conclusion: The supplement is recommended for COMPLETE RESPONSE. Deficiencies are listed on Page 29.

17. Name:	**Signature:**	**Date:**
Deepika Arora Lakhani, Ph.D., Chemist		**07/10/2013**

18. Concurrence:	**Signature:**	**Date:**
John Duan, Ph.D., Secondary Signature, Biopharmaceutics, ONDQA		**07/10/2013**
Ramesh Raghavachari, Ph.D., Acting Branch Chief, Div., IX, ONDQA		**07/10/2013**

Drug Product Information

1. Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. Each bottle of Nascobal (cyanocobalamin) Nasal Spray contains 2.3 mL of a 500 mcg / 0.1 mL solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water. The spray solution has a pH between 4.5 and 5.5.
2. 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 (cyanocobalamin) Nasal Spray.
3. Nascobal Nasal Spray was originally marketed in only one size. The original size consists of a bottle filled with 2.3 mL of cyanocobalamin solution. In April 2010, a supplement (S-011) was filed to add a new 1.5 mL fill volume size to the product line, and in December 2010, S-014 was filed to add a new 1.1 mL fill size. In this supplement, reduction of fill volume of the 1.1 mL fill to a 0.9 mL fill size is proposed.

Review of the Supplement

Currently, Nascobal® Nasal Spray is supplied in a multi-dose bottle. Nascobal is filled into 3 mL, (b) (4) glass bottles and closed with (b) (4) screw cap (b) (4). Each bottle of Nascobal® Nasal Spray is supplied with a nasal spray pump that is affixed to the bottle by the pharmacist at the time it is dispensed to the patient.

In this PAS, the Applicant is proposing the following change:

- Nascobal® Nasal Spray in a unit-dose device.
- The unit dose system consists of (b) (4).
- The device is designed to dispense 100 µL accurately.

Chemistry Assessment

(b) (4)

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IN VITRO BIOEQUIVALENCE

The objective of this study was to assess the potential bioequivalence of in vitro spray pump performance between Par Pharmaceuticals Nascobal (Cyanocobalamin) Nasal Spray in a multi-dose and a unit-dose device. In vitro spray pump performance was based on droplet size distribution (DSD) measured by Malvern SprayTec 2000, spray pattern (SP)/plume geometry (PG) measured by SprayVIEW NSP, and pump delivery (PD) measured gravimetrically (derived from DSD actuations). The data generated is shown below:.

(b) (4)

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(b) (4)

[redacted]

In Vitro BE Conclusion: The results from the bioequivalence study show that Par Pharmaceuticals Nascobal (Cyanocobalamin) Nasal Spray in a multi-dose (Reference) and a unit-dose (Test) device are not bioequivalent. In case of spray pattern, the bioequivalence criteria failed both for ovality ratio and area. Droplet size distribution (except for Span at a 6 cm tip-tolaser distance) and plume geometry do pass the bioequivalence criteria. The test pump will need to be modified or another pump should be considered for the Par Pharmaceuticals Nascobal (Cyanocobalamin) Nasal Spray to match the spray pattern of the reference pump. Furthermore, a study with a larger sample set may be a better indication of bioequivalence.
Further, the Applicant conducted In Vivo BE study to support the unit-dose.

IN VIVO BIOEQUIVALENCE STUDY

A BE Study was carried out to test equivalence between the proposed unit dose and the approved multi-dose product. The details of the study are outlined below:

Title: A Relative Bioavailability Study of a Test Unit- Dose Nasal Spray Delivery Device Containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.) Compared to NASCOBAL® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Distributed by: Strativa Pharm a Division of Par Pharm, Inc.) in Healthy Subjects under Fasted Conditions.

Study Duration: The time from first subject dosed to when the last subject completed was about 17 days.

Study Type: A randomized, single-dose, two-delivery system, two-treatment, two period, four-sequence, crossover study under fasting conditions.

Number of Subjects: A total of 24 healthy, adult subjects were enrolled, and 22 subjects completed both periods of the study.

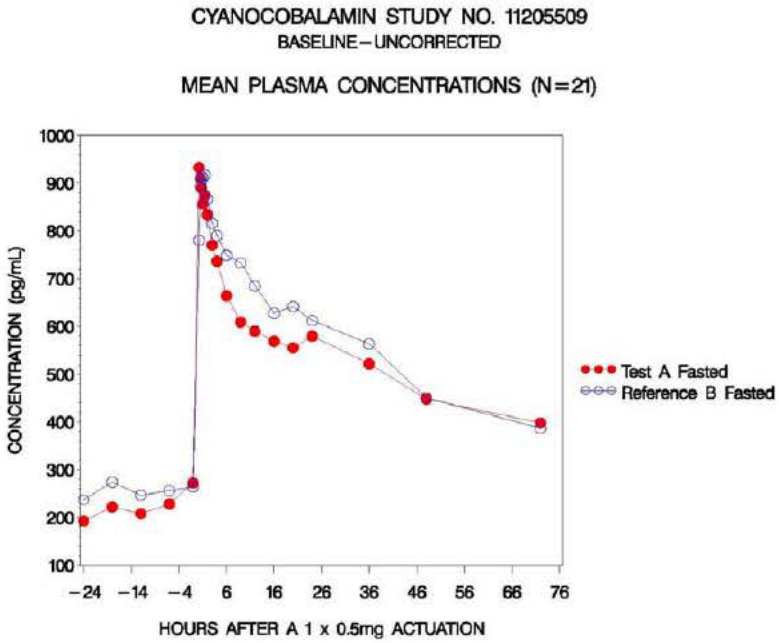
Method: The study enrolled 24 (22 completed both periods of the study) healthy, adult subjects in accordance. In each period, a 500 mcg dose (1 x 500 mcg/actuation; 1 spray into 1 nostril/period) of Nascobal® (was administered to each subject following an overnight fast of at least 10 hours. The test formulation was Nascobal® (cyanocobalamin, USP) 500 mcg/actuation nasal spray (Par Pharmaceutical, Inc.) from a unit-dose device and the reference formulation was NASCOBAL® (cyanocobalamin, USP) 500 mcg/actuation nasal spray from a multi-dose device. The subjects were dosed with the test device in one of the study periods and dosed with the reference device in the other study period according to a four-sequence randomization schedule. Subjects were confined at the clinical facility from at least 36 hours before dosing until after the 72-hour blood collection. The interval between doses was 14 days. Blood samples were collected from 24 hours pre-dose and at intervals over 72 hours after dosing in each period.

Statistical Methods: Twenty-two (22) blood samples were collected from each subject each period at -24, -18, -12, -6, and -1 hour (0 hour) pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 9, 12, 16, 20, 24, 36, 48, 72 hours post-dose. The analytical data was used to calculate the pharmacokinetic parameters: AUC_{0-t}, C_{max}, and T_{max}. The t in AUC_{0-t} is the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS, Version 9.2) was used for all pharmacostatistical calculations. Only subjects who completed both periods of the study had samples sent for bioanalytical analysis and were included in the pharmacostatistical analyses

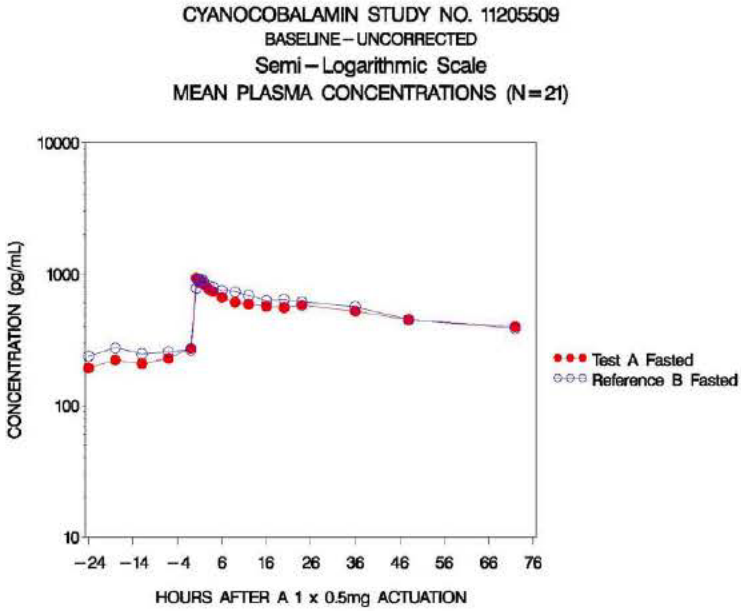
Summary of Results: Mean concentration-versus-time plots (linear and semilog) for baseline-uncorrected cyanocobalamin (primary bioequivalence) are shown below. Mean concentration-versus-time plots (linear and semi-log) for baseline-corrected cyanocobalamin (informational) are also shown below. The mean test-to-reference ratios for baseline-uncorrected cyanocobalamin and their associated 90% confidence intervals (primary bioequivalence) are

presented below. The mean test-to-reference ratios for baseline-corrected cyanocobalamin and their associated 90% confidence intervals (informational) are presented below.

Mean Plasma Concentration versus Time Plot (Linear): Baseline- Uncorrected Cyanocobalamin (Primary Bioequivalence)



Mean Plasma Concentration versus Time Plot (Semi-Log): Baseline- Uncorrected Cyanocobalamin (Primary Bioequivalence)

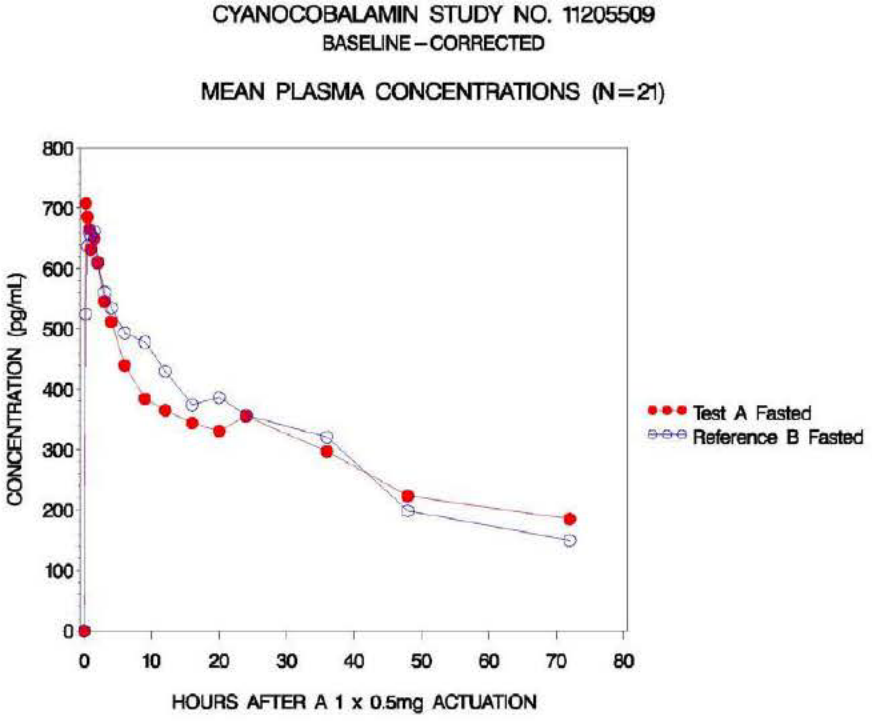


Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Baseline-Uncorrected Cyanocobalamin (Primary Bioequivalence)

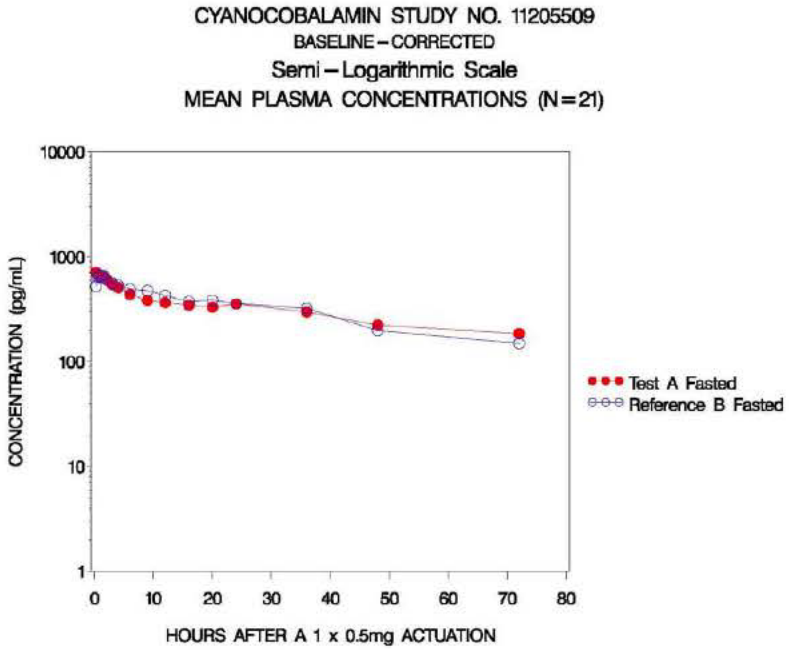
Parameter	Test A	Reference B	Ratio	CI**	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	31164.66	29428.96	1.0590	0.9208 - 1.2179	26.6343
Cmax (pg/mL) (N=21)*	858.98	859.21	0.9997	0.8711 - 1.1473	26.2127

*N=Number of subjects with evaluable data for both the test and reference products.
**Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Mean Plasma Concentration versus Time Plot (Linear): Baseline- Corrected Cyanocobalamin (Informational)



Mean Plasma Concentration versus Time Plot (Semi-Log): Baseline-Corrected Cyanocobalamin (Informational)



Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Baseline- Corrected Cyanocobalamin (Informational)

Parameter	Test A	Reference B	Ratio	CI	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	17788.15	14955.73	1.1894	0.8092 - 1.7483	82.5776
Cmax (pg/mL) (N=21)*	674.57	648.84	1.0397	0.8784 - 1.2305	32.3513

*N=Number of subjects with evaluable data for both the test and reference products.

Evaluation: INADEQUATE. The Applicant was sent the following IR comments on June 11, 2013 upon review of the BE study. The Applicant responded to the IR via an amendment dated June 28, 2013.

1. Provide the $AUC_{0-\infty}$ for both the uncorrected and baseline-corrected cyanocobalamin data. Provide the following PK parameters for both the uncorrected and baseline-corrected cyanocobalamin data: $t_{½}$, λ_z.

2. Comment on the failure of BE for the upper bound of the 90% CI for $AUC_{(0-t)}$ for the baseline corrected cyanocobalamin data.

For the baseline-corrected $t_{½,z}$, λ_z and $AUC_{0-\infty}$ parameters, the Applicant responded that the elimination PK parameters, $t_{½,z}$ (apparent terminal elimination half-life) and λ_z (apparent terminal elimination rate constant), and associated $AUC_{0-\infty}$ parameter, were not estimated in study

11205509, as per protocol, because the clinically relevant terminal half-life for cyanocobalamin was expected to be very long (about 7 days) relative to the proposed blood sampling duration of 72 hours. This would lead to unreliable estimations of $AUC_{0-\infty}$ owing to large extrapolated portions of > 20% (i.e., AUC_{0-t} /$AUC_{0-\infty}$ < 80%).

In study 11205509, AUC_{0-t} (t = 72 hours) was used in place of $AUC_{0-\infty}$ to compare the bioavailability of cyanocobalamin from a new test device of Nascobal® (cyanocobalamin, USP) 500 mcg/actuation nasal spray (Par Pharmaceutical, Inc.) with that of the approved multi-dose NASCOBAL® (cyanocobalamin, USP) 500 mcg/actuation nasal spray.

As the intra-subject variability for baseline-corrected C_{max} and AUC parameters was high (> 30%), the truncation of AUC to 72 hours, would be preclude. The high variability is a consequence of the baseline correction and the associated high contribution of basal concentrations to total post-dose cyanocobalamin concentrations. Therefore, the Applicant was of the opinion that truncation of AUC to 72 hours is warranted and estimations of $t_{½,z}$, λ_z and $AUC_{0-\infty}$ parameters would give unreliable results, particularly considering the duration over which the λ_z would be typically estimated (i.e., 48 hours from 24 to 72 hours post-dose) is less than the expected 7-day half-life of cyanocobalamin.

For the baseline-uncorrected $t_{½,z}$, λ_z and $AUC_{0-\infty}$ parameters, the Applicant responded that as cynacobalamin is also present endogenously the estimation of λ_z and associated PK parameters that are dependent on reliable estimations of λ_z, such as $t_{½,z}$ and $AUC_{0-\infty}$, is pharmacokinetically appropriate for only baseline-corrected data. For baseline-uncorrected data, the terminal phase of the concentration versus time plot from the exogenous administration is a composite of concentrations from both exogenously administered drug and from the basal concentrations of the endogenous component of the drug, such that the terminal rate constant (λ_z) determined from the slope of the terminal phase of the log concentration-time plot is not a pure function of drug elimination. Therefore, use of this rate constant to calculate $t_{½,z}$ and the extrapolated portion of $AUC_{0-\infty}$ is not recommended. Eventually the concentrations of the exogenously administered drug will decrease to the baseline concentrations and theoretically $AUC_{0-\infty}$ is equal to infinity. Hence, these values were not provided.

To explain the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data, the Applicant responded that this is a direct result of the high intra-subject variability for this parameter owing to the high baseline contribution of endogenous to total post-dose cyanocobalamin concentrations. The baseline contribution to AUC_{0-t} was 43% for test treatment and 45% for reference treatment with exclusion of subject 20 (n = 21). Adjustment of the post-dose concentrations for baseline contribution increased the intra-subject variability for AUC_{0-t} from 27% (uncorrected) to 83%.

The assay lower limit of quantitation (LLOQ) was 200 pg/mL. The main problem when pre-dose concentrations approach the LLOQ is that some subjects will have a baseline correction in one period but not in the other or some pre-dose concentrations will be below the LLOQ (BLOQ) and others will be >LLOQ, as was observed in study 11205509. This all contributes to the high intra-subject CV in baseline-corrected AUC. In this study 7 of 22 subjects (test) and 8 of 22 subjects (reference) that completed both periods of the study had a mixture of at least one BLOQ pre-dose concentration and a measureable pre-dose concentration for the five pre-dose samples (-

24, -18, -12, -6 and -1 hour). This mixture of BLOQ and measureable pre-dose concentrations for these subjects potentially led to inaccurate estimations of the mean of the five pre-dose concentrations that was used to correct the post-dose concentrations. This could have subsequently led to corresponding inaccurate baseline adjustment and to the associated high observed intra-subject variability in the baseline-corrected AUC_{0-t}. There is no suitable baseline correction method that can accurately compensate for this potential inaccuracy in baseline adjustment from the mixture of BLOQ and measureable pre-dose concentrations.

OVERALL BIOPHARMACEUTICS CONCLUSION: The Applicant justifies the failure of BE for baseline-corrected data based on the high intra-subject variability, primarily attributable to the endogenous presence of cynacobalamin. However, based on the 24 hour baseline levels of cynacobalamin provided, the variability does not appear to be high in the endogenous levels to result in failure of BE. Therefore, at this stage, the present study cannot be approved and the products cannot be deemed bioequivalent. The Applicant will be requested to clarify this and provide more data points for the baseline cynacobalamin.

DEFICIENCIES

1. The justification provided to explain the failure of BE for the upper bound of the 90% CI for $AUC_{(0-t)}$ for the baseline corrected cyanocobalamin data is not acceptable. Based on the review of the baseline cynacobalamin data provided for the 24 hours prior to the administration of the dose, the levels of endogenous cynacobalamin do not have very high variability. To support and justify the failure of BE for corrected data, we recommend that you provide data to support the inherent variability of endogenous cynacobalamin, for example, basal cynacobalamin levels for 72 hours.

2. Clarify if any degradation products from benzalkonium chloride were observed during the inverted accelerated stability studies (b) (4) [redacted]

Attachment

Nanotechnology Submission Report Form

Nanotechnology is absent.

Report # (For WG internal use)	
Application and submission number (*e.g.*, I-XXXXXX-P-XXXX)	21-642/S-020
Who has identified the product as a potential for containing nanomaterials? (i.e. Sponsor or CVM)	Nanotechnology not present
Is this a modification of an approved product or another investigational product? If so, what has been modified?	No
Please describe the nanomaterials (*e.g.*, poloxamer 188 micelle with emulsified active, particle size 30 -50 nm, or nanocrystal suspension, particle size 130 – 160 nm, etc.)	None
Does the new formulation have unique properties including effects via engineering of the constituent on the nanoscale? If so, explain.	No
Other information worth recording (*e.g.*, INAD or NADA # of a corresponding product w/o nanomaterials)	No
Reviewer Name, Date, HFV code	Deepika Arora Lakhani, 10-JULY-2013

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

/s/

DEEPIKA LAKHANI
07/11/2013
Complete Response is recommended.

JOHN Z DUAN
07/11/2013

RAMESH RAGHAVACHARI
07/11/2013
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021642Orig1s020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 21642/S-020 Resubmission (SDN 40)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DMP		
Applicant:	Par Pharmaceuticals, Inc.	**Team Leader:** Angelica Dorantes, Ph.D. .	
Trade Name:	Nascobal Nasal Spray	**Supervisor (acting):** Richard Lostritto, Ph.D.	
Generic Name:	Cyanocobalamin Nasal Spray	**Date Assigned:**	Nov 6, 2013
Indication:	Maintenance of normal hematologic status in pernicious anemia	**Date of Review:**	April 21, 2014
Formulation/strengths	Nasal Spray, 500 mcg/spray		
Route of Administration	Nasal		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**PDUFA Date**
Oct 25, 2013	Oct 25, 2013	Feb 25, 2014

Type of Submission:	ADDENDUM to Complete Response to S020 Submission
Type of Consult:	BE and Population PK analysis

SUMMARY OF BIOPHARMACEUTICS FINDINGS-ADDENDUM

This is an addendum to the Original Biopharmaceutics review by Dr. Sandra Suarez Sharp entered in DARRTS on Jan 30, 2014. An APPROVAL action was recommended in the Original review which included the following comments to be conveyed to the Applicant:

1. *Your request to fulfill the Postmarking Commitment within 6 to 12 months from the approval date of this supplement is acceptable. However, we have the following recommendations in terms of the study design for assessing the cyanocobalamin concentrations at steady state following administration of your drug product:*

(b) (4)

[redacted]

On April 21, 2014, a meeting was held between members of the ONDQA-Biopharmaceutics team and the DMEP Clinical team. During this meeting the rationale behind the need for a PMC and the use/benefit of the data generated under this PMC were thoroughly discussed. It was concluded that the need for a PMC is not justified and therefore, a PMC is not longer necessary for the following reasons:

1. The cyanocobalamin Cmin levels following single dosing administration were higher for the

product under review compared to the approved product; therefore, it is unlikely that the levels at steady state will be lower for Nascobal® unit-dose nasal spray;
2. The cyanocobalamin levels are routinely monitored, so if the levels are below or above the desired plasma level the dose will be adjusted as necessary (refer to Nascobal Approved Label);
3. The computer simulations done internally by this Reviewer and by the Applicant suggest that it is likely that the cyanocobalamin Cmin steady state levels will be higher than 200 pg/mL.
4. The 20% higher AUC value observed in BE Study 11205509 for the product under review is not of safety concern given that higher levels have been reported for the approved product. In addition, based on the Applicant's comparative predictions in AUC and Cmax values for both products, repeated administration of the two products is expected to result in similar safety under steady-state conditions.

RECOMMENDATION:
ONDQA-Biopharmaceutics has reviewed the Resubmission of NDA 21642/PAS-020 for Nascobal® unit-dose nasal spray delivery dated October 25, 2013. From a Biopharmaceutics perspective, this Supplement is recommended for APPROVAL. The following comment should be conveyed to the Applicant:

1. Upon further consideration and based on the results of your population PK analysis, the FDA considers that the conduct of a PMC for Nascobal® unit-dose nasal spray is not longer needed.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

c.c. RLostritto;

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

/s/

SANDRA SUAREZ
04/21/2014

ANGELICA DORANTES
04/21/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 21642/S-020 Resubmission (SDN 40)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DMP		
Applicant:	Par Pharmaceuticals, Inc.	**Team Leader:** Angelica Dorantes, Ph.D. .	
Trade Name:	Nascobal Nasal Spray	**Supervisor (acting):** Richard Lostritto, Ph.D.	
Generic Name:	Cyanocobalamin Nasal Spray	**Date Assigned:**	Oct 6, 2013
Indication:	Maintenance of normal hematologic status in pernicious anemia	**Date of Review:**	January 28, 2014
Formulation/strengths	Nasal Spray, 500 mcg/spray		
Route of Administration	Nasal		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**PDUFA Date**
Oct 25, 2013	Oct 25, 2013	Feb 25, 2014

Type of Submission:	Complete Response to S020 Submission
Type of Consult:	BE and Population PK analysis

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Background: Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. Nascobal 500 mcg/spray, Nasal Spray was approved by the FDA on January 31, 2005, for the maintenance of normal hematologic status in pernicious anemia. Each bottle of Nascobal Nasal Spray contains 2.3 mL of a 500 mcg / 0.1 mL solution of cyanocobalamin (multi-dose bottle). The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly.

On March 12, 2013, the Applicant submitted a Post Approval Supplement (S-020) seeking approval of Nascobal® Nasal Spray in a unit-dose device. In support of this change, the Applicant included CMC information, in vitro BE data and the results of an in vivo bioequivalence study comparing the Unit- Dose Nasal Spray Delivery Device Containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.) to NASCOBAL® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray. The results of the in vivo BE study showed lack of bioequivalence (the 90% CI were out of the 80-125 goal post for AUCt (0.800-1.748) for the baseline-corrected cyanocobalamin data. The Applicant attributed the failed BE result to a large intra-subject variability, primarily due to the endogenous presence of cyanocobalamin. A complete Response (CR) letter was issued on July 12, 2013, for this supplement listing several biopharmaceutics deficiencies[1].

On August 5, 2013, an Email correspondence was submitted by the Applicant containing a further

[1] CMC and Biopharmaceutics review entered in DARRTS by Deepika Lakhani on 7/11/2013.

explanation/justification for the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data based on an additional analysis conducted. Upon review[2] and internal discussion with the clinical team on the Applicant's proposal, the following comments were conveyed to the Applicant on 09/30/13:

1. Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:
   a. Provide information/data (e.g. modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at Steady State are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
   b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.
   c. A post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this Supplement.

In addition, several recommendations were included for the conduct of any future BE studies involving the proposed cyanocobalamin nasal spray product.

On October 15, 2013, the Applicant submitted an email communication requesting clarification for some of the deficiency comments sent on 09/20/13. The FDA's response to this communication dated Oct 31, 2013, can be found in DARRTS[3].

Current Submission

The current submission is a resubmission of PAS-020 after a CR action. It provides the Applicant's complete response to the July 12, 2013 CR action letter and additional FDA's comments sent to them on Aug 5 and Oct 31, 2013. The following summarizes the Applicant's responses:

1. **Data Supporting the Cyanocobalamin Steady State Concentrations Following Multiple Dose Administration Using the Proposed Product**

The Applicant provided information/data from population PK (PopPK) modeling and simulations using data from previously reported BE study 11205509. The analysis showed that the baseline-unadjusted pre-dose trough concentrations are predicted to be above 200 pg/mL in patients with a vitamin B12 deficiency (assumed to be 100 pg/mL) following multiple-dose administration of the proposed product (unit-dose nasal spray delivery device containing Nascobal®).

2. **Justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.**

The Applicant provided a reasonable explanation for this observation, stating that this phenomenon is due to the way the mean values are calculated for data plotting versus the way the data are averaged for statistical analysis. In other words, AUC0-t (t = 72 hr) geometric test and reference means are based on the

[2] Biopharmaceutics Review entered in DARRTS by Sandra Suarez on 09/17/2013

[3] Biopharmaceutics Review for communication received 10/15/13 entered in DARRTS by Sandra Suarez on 10/25/2013 (http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3396772&fromHistoryPage=true&appPk=114458).

average on individual AUC values, whereas the apparent AUC0-72 observed from the mean concentration-time profile is a composite of the mean concentrations at each of the sampling times.

3. Post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device.

Par responded that they commit to conducting a post-market study to monitor the levels of cyanocobalamin at steady state following administration of the product with the new device. However, the Applicant requests the Agency to allow them to fulfill this commitment within 6 to 12 months of the approval of this supplement. A brief description on the study design (b) (4) was also included.

The Applicant's request is acceptable in terms of the time period proposed to fulfill the commitment (e.g. 6 to 12 months from approval date of this supplement). However, we have several recommendations (see below) for the Applicant in terms of the study design for their consideration.

RECOMMENDATION:
ONDQA-Biopharmaceutics has reviewed the Resubmission of NDA 21642/PAS-020 for Nascobal® unit-dose nasal spray delivery dated October 25, 2013. From a Biopharmaceutics perspective, this Supplement is recommended for APPROVAL.

The following comments should be conveyed to the Applicant:

1. *Your request to fulfill the Postmarking Commitment within 6 to 12 months from the approval date of this supplement is acceptable. However, we have the following recommendations in terms of the study design for assessing the cyanocobalamin concentrations at steady state following administration of your drug product:*

(b) (4)

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

c.c. RLostritto;

BIOPHARMACEUTICS FINDINGS
Background

Cyanocobalamin is a synthetic form of vitamin B12 with equivalent vitamin B12 activity. Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. The Applicant developed a new nasal spray delivery device that delivers a unit dose of cyanocobalamin 0.5 mg/nasal spray 0.1 mL spray solution. The new unit-dose device contains 125 µL of cyanocobalamin solution intended for a single administration to deliver 0.1 mL solution /actuation. The formulation is the same between the new unit-dose container and the currently approved and marketed multi-dose Nascobal® (cyanocobalamin) 0.5 mg/nasal spray 0.1 mL spray solution.

In support of the proposed product, a randomized, single-dose, two-treatment, two-period, crossover study was conducted to compare the bioavailability of cyanocobalamin from a new test device of cyanocobalamin unit-dose nasal spray, 0.5 mg/spray with that of the already approved Nascobal® (cyanocobalamin) nasal spray, 0.5 mg/spray in healthy subjects (n=24) under fasting conditions. One (1) actuation of 0.1 mL (0.5 mg cyanocobalamin)/spray was dosed as a single spray into a single nostril, in each period of this study (Study Protocol 11205509).

The results of this in vivo BE study showed lack of bioequivalence (the 90% CI were out of the 80-125 goal post for AUCt (0.800-1.748) for the baseline-corrected cyanocobalamin data. The Applicant attributed the failed BE result to a large intra-subject variability, primarily due to the endogenous presence of cyanocobalamin. A CR letter was issued on July 12, 2013, for this supplement listing several biopharmaceutics deficiencies. Reference is also made to the email correspondence from the Applicant dated Aug 15, 2013 and Oct 15, 2013 requesting further feedback on the data to be included in the complete response.

The current submission contains the Applicant's responses to the following comments included in the information request dated 09/30/13.

1. Provide information/data (e.g. modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at Steady State are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
2. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.
3. A post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this Supplement.

RESPONSES

1. **Data Supporting the Cyanocobalamin Steady State Concentrations (Cmin and Cmax) Following Multiple Dose Administration Using the Proposed Product**

Population PK MODEL FOR BASELINE-CORRECTED CYANOCOBALAMIN

Plasma concentration-time profiles of cyanocobalamin from a total of 22 healthy subjects (Study (Study Protocol 11205509) treated with test and reference products were used to construct a population PK model. Baseline-corrected concentrations were used for the modeling. Baseline levels were derived by averaging the five pre-dose plasma concentrations of cyanocobalamin in each period. Baseline-correction was performed by subtracting individual post-dose concentrations for each subjects by their respective baseline values in each period. Values below the lower limit of assay quantitation (200 pg/mL) were set to missing for the population PK analysis. Mean plasma concentration-time profiles of baseline-adjusted cyanocobalamin are presented in Figure 1.

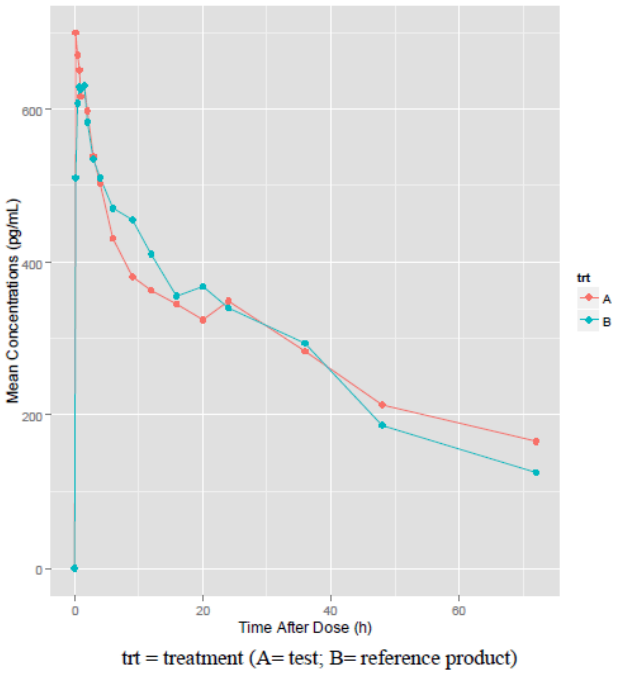


Figure 4.1 Mean Baseline-Corrected Plasma Concentration-Time Profiles of Cyanocobalamin for the Test and Reference Products (Linear Scale).

A 2-compartement model with formulation effect (Frel) (best quality of fit; refer to \\CDSESUB1\evsprod\NDA021642\0015\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\parp-pcs-100 for details on model performance), was used to model the concentration-time profiles of cyanocobalamin and perform simulations to determine steady-state drug exposure.

Model validation was based on model diagnostic plots and related statistical calculations. The following diagnostic plots were performed among other statistical calculations:

- Observed Data versus Population Predicted Data (DV vs. PRED) and versus Individual Predicted Data (DV vs. IPRED) with a line of unity and a trend line.
- Conditional weighted residuals versus Predicted Data (CWRES vs. PRED) with zero line and a trend line.
- Conditional weighted residuals versus Time or Time after Dose (CWRES vs. Time or time after dose) with zero line and a trend line.

Individual predicted concentrations of cyanocobalamin were well fitted with the 2-compartment model (Figure 2).

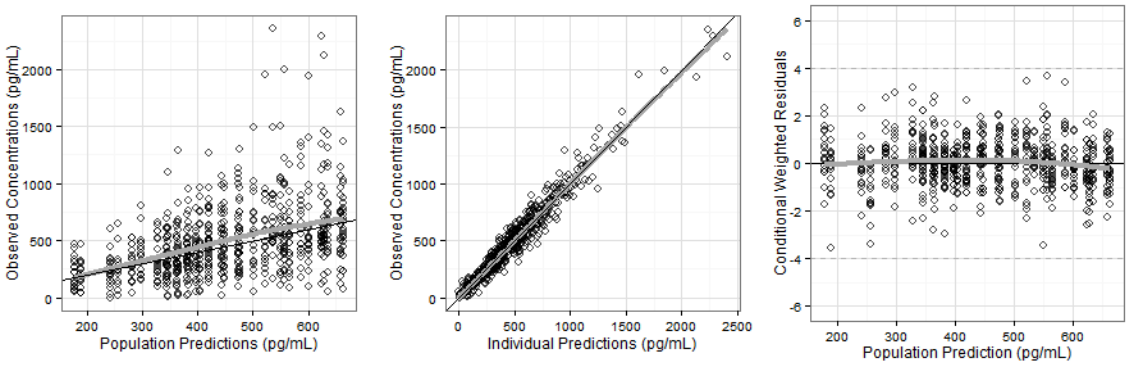


Figure 2. Goodness of Fit - Population PK Model - Baseline-Corrected Plasma Concentrations of Cyanocobalamin.

POPULATION PK MODEL REFINEMENT AND TERMINAL ELIMINATION HALFLIFE OF CYANOCOBALAMIN

The population PK model was refined based on publicly available data in order to adequately capture the true terminal elimination of cyanocobalamin. Typical population values of CL/F and Vc/F of cyanocobalamin were 0.00713 L/h and 0.635 L, respectively. The half-life associated to the beta phase (t1/2) was 174 h.

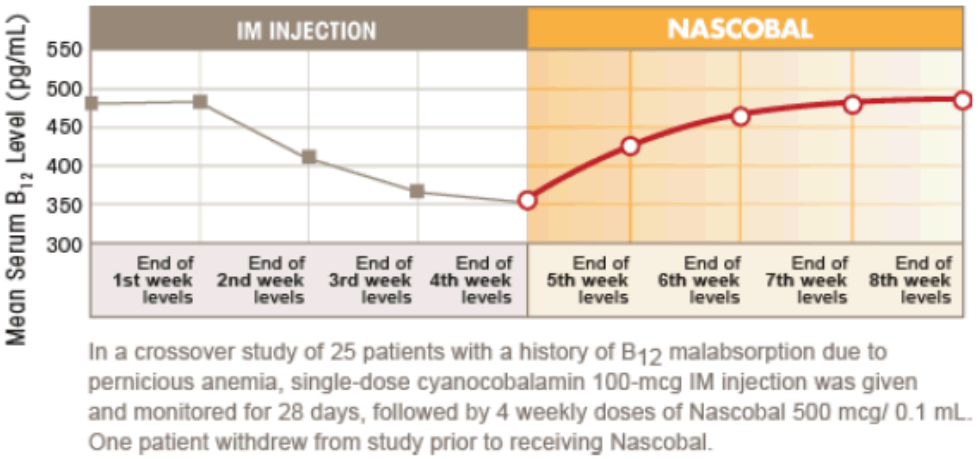


Figure 3. Vitamin B12 Serum Trough Levels Reported in the Nascobal® Product Label.

Based on data from Figure 3, a values of 7 days (168 h) as an estimated IN clinically relevant, terminal elimination half-life was deemed appropriate for modeling. The refined typical population PK parameters are not shown in here (refer to Table 4.3 on the following link: \\CDSESUB1\evsprod\NDA021642\0015\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\parp-pcs-100).

The half-life associated to the alpha and beta phases (t1/2 and t1/2) were 8.95 and 174 h, respectively. The t1/2 derived with the model was consistent with the value extracted from the literature (174 vs. 168 h). The goodness-of-fit of the final population PK model showed that the model accurately predicted the observed data (Figure 4).

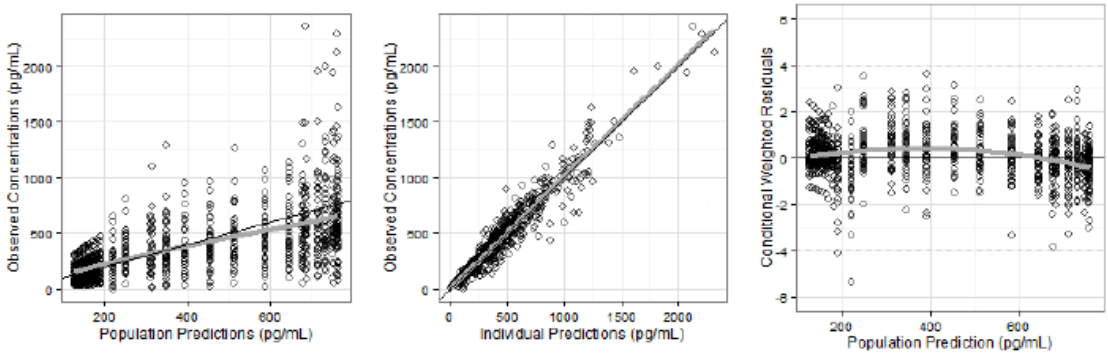


Figure 4. Goodness of Fit for refined Population PK Model - Baseline-Corrected Plasma Concentrations of Cyanocobalamin.

SIMULATIONS IN PATIENTS WITH LOW BASELINE VITAMIN B12 LEVELS

The final population PK model was used to perform simulations and predict drug exposure under steady state conditions after once-weekly IN administrations of the test

and reference products. Exposure to cyanocobalamin in patients with low baseline values of vitamin B12 was derived.

A literature review was performed was performed by the Applicant to assess typical baseline levels of vitamin B12 in patients with cobalamin deficiency. Based on the literature review, a typical baseline level of 100 pg/mL was used for the simulations.

For patients with expected baseline vitamin B12 levels of 100 pg/mL, mean cyanocobalamin Cmin values following repeated administration of the test and reference products were predicted to be 344 and 345 pg/mL, respectively (Table 1). The probability of Cmin ≥200 pg/mL at steady state was 97.5 % for the test product. Descriptive statistics of predicted Cmax under steady-state conditions are presented in Table 2.

Table 1. Predicted Steady-State C_{min} Values of Cyanocobalamin in Patients with Low Baseline Levels of Vitamin B_{12}

Baseline Vitamin B_{12}	**Descriptive Statistics**	**C_{min} (pg/mL)**	
		Test (Par Pharmaceutical)	**Reference (Nascobal®)**
100 pg/mL	Median	349	349
	Mean	**344**	**345**
	95% CI Lower Limit	201	201
	95% CI Upper Limit	464	465
	Probability ≥200 pg/mL	97.5	97.5

CI = confidence interval; C_{max} = maximum concentration

Table 2. Predicted Steady-State C_{max} Values of Cyanocobalamin in Patients with Low Baseline Levels of Vitamin B_{12}

Baseline Vitamin B_{12}	**Descriptive Statistics**	**C_{max} (pg/mL)**	
		Test (Par Pharmaceutical)	**Reference (Nascobal®)**
100 pg/mL	Median	1087	1089
	Mean	**1988**	**1992**
	95% CI Lower Limit	377	378
	95% CI Upper Limit	8900	8917

CI = confidence interval; C_{max} = maximum concentration

Reviewer's Comments

The Population PK model constructed to predict baseline-unadjusted cyanocobalamin concentrations at steady state considered the following assumptions:

1. *The clinically relevant half-life of cyanocobalamin of 7 days which explains drug accumulation to steady and is longer than the terminal half-life estimated from the single-dose study 11205509, and*
2. *An average baseline concentration to be expected in patients with low cyanocobalamin concentrations of 100 pg/mL.*

The need for the determination of the clinically relevant half-life was warranted because: 1) the terminal rate constant λz could not be accurately calculated given that sampling was done only for 72 hrs after dosing, and 2) even for the reliable estimates of λz, the estimated half-lives (< 30 hours) were not the clinically relevant or physiologically effective, as they would be too short to explain the expected drug accumulation over 4 weeks to steady state following once-weekly intra-nasal dosing of cyanocobalamin-containing nasal spray products[4]. Therefore, this Reviewer concurs with the Applicant's approach in refining the PopPK model based on estimations of the half-life using published literature.

In general, the goodness of fit and internal validation confirms the robustness of the predictive model. Also the model confirmed this Reviewer's findings in terms of the estimated steady state concentration following multiple dose administration of the prosed product. Using Phoenix Software and assuming a half-life of 100 hrs, the simulations run by this Reviewer predicted, that following multiple dose (weekly) administrations of 500 mcg/spray, the baseline-corrected cyanocobalamin Cmin would be above 200 pg/mL (see Figure 5 below).

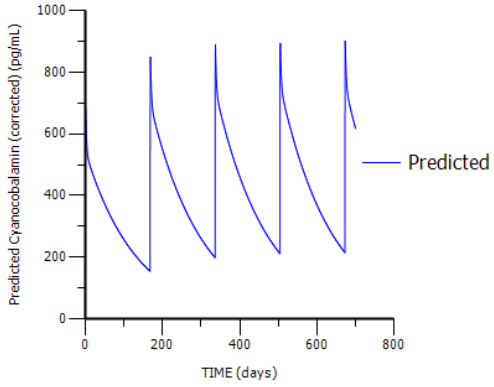


Figure 5. Predicted baseline corrected cyanocobalamin plasma concentrations following multiple dose (weekly) administrations of 500 mcg/spray.

[4] Product Label for Nascobal® (Cyanocobalamin, USP) Nasal Spray, 500 mcg/spray. Par Pharmaceutical Companies, Inc.

The Cmax (Table 2) and AUC0-tau (not shown in here) values predicted for the test formulation were nearly identical to those predicted for the reference product, suggesting that repeated administration of the test and reference products will result in similar exposure under steady-state conditions in patients with low vitamin B12 levels. These results also answer the question raised in terms of any potential safety concerns following multiple dose administration of the proposed product.

2. **Justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.**

According to the Applicant, this phenomenon is explained by the averaging effect of the mean concentrations at each of the sampling times compared to the averaging effect of the individual PK parameters. AUC_{0-t} (t = 72 hr) geometric test and reference means are based on the average on individual AUC values, whereas the apparent AUC_{0-72} observed from the mean concentration-time profile is a composite of the mean concentrations at each of the sampling times.

3. **A post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this Supplement.**

Par responded that they commit to conducting a post-market study to monitor the levels of cyanocobalamin at steady state following administration of the new device.

Reviewer's Comments
The Applicant's request is acceptable, in terms of the period of time to fulfill the commitment (e.g. 6 to 12 months from the approval date of this supplement). However, we have the following comments which consider the clinical team's input:


(b) (4)

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/s/

SANDRA SUAREZ
01/30/2014

ANGELICA DORANTES
01/30/2014

BIOPHARMACEUTICS REVIEW- ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 21642 S-020 (SDN 322 and 329)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DMP		
Applicant:	Par Pharmaceuticals, Inc.	**Team Leader:** Angelica Dorantes, Ph.D. .	
Trade Name:	Nascobal Nasal Spray	**Supervisor (acting):** Richard Lostritto, Ph.D.	
Generic Name:	Cyanobalamin Nasal Spray	**Date Assigned:**	Aug 15, 2013
Indication:	Maintenance of normal hematologic status in pernicious anemia	**Date of Review:**	Oct 24, 2013
Formulation/strengths	Nasal Spray, 500 mcg/spray		
Route of Administration	Nasal		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Desired Completion Date**
Email-Correspondence Oct15, 2013	Oct 15, 2013	Oct 24, 2013
Type of Submission:	Correspondence/Request for clarification	
Type of Consult:	Biopharmaceutics data needed to support the proposed manufacturing changes	

SUMMARY:

This document is an addendum to the original Biopharmaceutics review dated September 17, 2013 by Dr. Sandra Suarez.

Background: Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. Nascobal 500 mcg/spray, Nasal Spray was approved by the FDA on January 31, 2005, for the maintenance of normal hematologic status in pernicious anemia. Each bottle of Nascobal Nasal Spray contains 2.3 mL of a 500 mcg / 0.1 mL solution of cyanocobalamin (multi-dose bottle). The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly.

On March 12, 2013, the Applicant submitted a Post Approval Supplement (S-020) seeking approval of Nascobal® Nasal Spray in a unit-dose device. In support of this change, the Applicant included CMC information, in vitro BE data and the results of an in vivo bioequivalence study comparing the Unit- Dose Nasal Spray Delivery Device Containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.) to NASCOBAL® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray. The results of the in vivo BE study showed lack of bioequivalence (the 90% CI were out of the 80-125 goal post for AUCt (0.800-1.748) for the baseline-corrected cyanocobalamin data. The Applicant attributed the failed BE result to a large intra-subject variability, primarily due to the endogenous presence of cyanocobalamin. A CR letter was issued on July 12, 2013, for this supplement listing several biopharmaceutics deficiencies[1].

On August 5, 2013, an Email correspondence was submitted by the Applicant containing further

[1] CMC and Biopharmaceutics review entered in DARRTS by Deepika Lakhani on 7/11/2013.

explanation/justification for the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data based on additional analysis conducted. Upon review[2] and internal discussion with the clinical team on the Applicant's proposal, the following comments were conveyed to the Applicant on 09/30/13:

1. Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:
    a. Provide information/data (e.g. modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at Steady State are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
    b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.
    c. A post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this Supplement.

In addition, several recommendations were included for the conduct of any future BE studies involving the proposed cyanocobalamin nasal spray product.

Current Submission

On October 15, 2013, the Applicant submitted an email communication requesting clarification for some of the deficiency comments sent on 09/20/13. This addendum to the original Biopharmaceutics review contains the Reviewer responses to this clarification request (see appendix for additional details).

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the email communication received on October 15, 2013 for Supplement 20 (SDN 322 and 329) under NDA 21642 and has the following responses for the Applicant's clarification questions.

RESPONSES TO BE CONVEYED TO THE APPLICANT:

1. **Does the Agency concur with the above approach to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency?**

FDA Response:

Given the constrains in obtaining a reliable half-life following single administration of the product and the uncertainty in terms of whether after nasal administration the cyanocobalamin plasma concentrations are the result of nasal absorption only or both nasal and GI absorption which may be different in the patient population vs. healthy volunteers we request that you

[2] Biopharmaceutics Review entered in DARRTS by Sandra Suarez on 09/17/2013

provide the following information under a post marketing commitment:

a. *Report the baseline and steady state concentrations after one month of multiple dosing of cyanocobalamin in a representative number of patients with chronic B12 deficiency receiving the new drug product, Nascobal® Nasal Spray in a unit-dose device.*

2. Par requests clarification if the Agency is requesting provision of a justification as to why the cyanocobalamin AUC_{0-t} (t = 72 h) geometric T/R ratio for unadjusted concentration data, as determined from the analysis of variance (Table 11.4.1.3 in the clinical study report), is higher at 1.0590, despite its lower mean concentration-time profile pre- and post-administration (Figure 14.2.1 in the clinical study report). Or is the Agency requesting provision of a justification as to why the cyanocobalamin AUC_{0-t} (t = 72 h) geometric T/R ratio for baseline-corrected concentration data, as determined from the analysis of variance (Table 11.4.1.6 in the clinical study report), is higher at 1.1894, despite its lower mean concentration-time profile pre- and post-administration (Figure 14.2.3 in the clinical study report).

FDA Response:
Explain why the AUCt after the administration of the test (31164.66 pg/h/mL) is higher than the reference (29428.96 pg/h/mL), when the profile in Figure 14.2.1 for the test is lower than that for the reference.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

c.c. RLostritto;

APPENDIX (Document submitted on Oct 15, 2013 via email)

1. **Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:**
   a. **Provide information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at steady state are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.**

Therapeutic drug monitoring for patients with vitamin B_{12} deficiency, as recommended in the Nascobal® product label, are based on actual observed blood concentrations of cyanocobalamin. Therefore, Par requests clarification if the Agency is requesting provision of information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the **baseline-unadjusted** cyanocobalamin **trough** concentrations are above 200 pg/mL **in patients with a vitamin B_{12} deficiency following multiple-dose administration of the test unit-dose nasal spray delivery device containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.)**? The single-dose study (in the Summary Basis for Approval of Nascobal® NDA-21-642) and Par's single-dose study 11205509 were conducted in healthy volunteers. Therefore, if the Agency concurs with the above, Par proposes to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency. Because the average baseline cyanocobalamin concentrations are > 200 pg/mL in the healthy volunteers who participated in study 11205509 (i.e., 234 pg/mL in period 1 and 224 pg/mL in period 2 using 0 as the imputation for BLOQ values), both baseline-corrected and baseline-uncorrected data will be modeled.

A reliable estimate of the clinically relevant terminal elimination half life ($t_{½,z}$) is required to predict steady-state concentrations from single-dose data. However, the $t_{½,z}$ values estimated in study 11205509 were deemed unreliable for most data sets, as explained in the correspondence emailed to FDA on August 26, 2013 (Par's Discussion Points for study 11205509, Amendment 1). In study 11205509 the reliable estimates all have associated $t_{½,z}$ values that are < 30 hours, but these values are likely underestimated because of the short sampling duration (72 h) relative to the 7-day dosing period. In Par's previous correspondence dated June 28, 2013, we estimated the clinically relevant half-life as 7 days from the 4-week multiple-dose Nascobal® nasal gel data presented as a graph in the product label. We propose to use a 7-day half-life for the modeling of the single-dose data.

Does the Agency concur with the above approach to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted

cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency?

b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite its lower concentration-time profile pre- and post-administration.

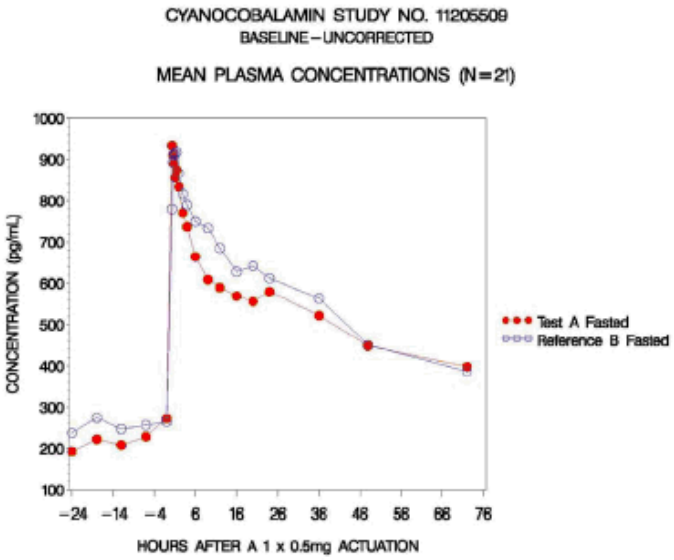
Par requests clarification if the Agency is requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 h) geometric T/R ratio for unadjusted concentration data, as determined from the analysis of variance (Table 11.4.1.3 in the clinical study report),** is higher **at 1.0590**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.1 in the clinical study report).**

Table 11.4.1.3 Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Baseline-Uncorrected Cyanocobalamin-Primary Bioequivalence

Parameter	Test A	Reference B	Ratio	CI**	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	31164.66	29428.96	1.0590	0.9208 - 1.2179	26.6343
Cmax (pg/mL) (N=21)*	858.98	859.21	0.9997	0.8711 - 1.1473	26.2127

*N=Number of subjects with evaluable data for both the test and reference products.
**Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Figure 14.2.1 Mean Plasma Concentration versus Time Plot (Linear): Baseline-Uncorrected Cyanocobalamin (Primary Bioequivalence)



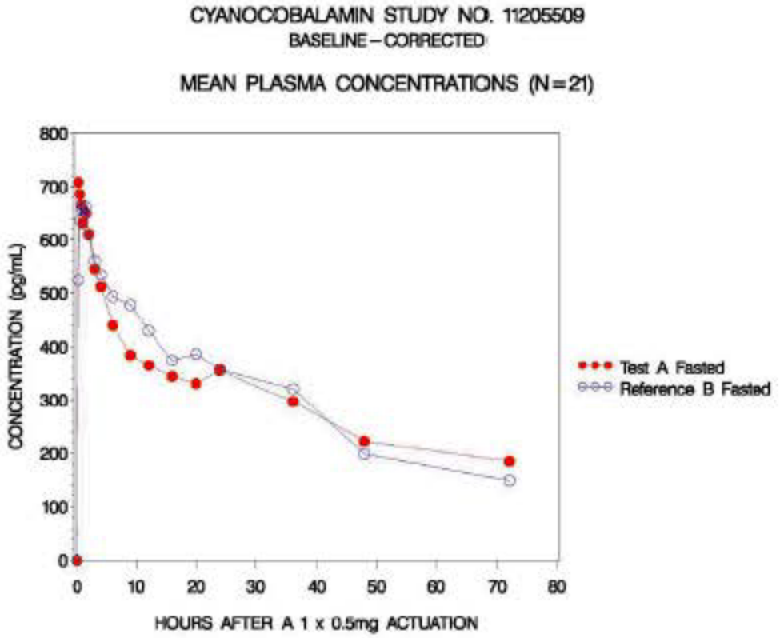
Or is the Agency requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 h) geometric T/R ratio for baseline-corrected concentration data, as determined from the analysis of variance (Table 11.4.1.6 in the clinical study report),** is higher **at 1.1894**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.3 in the clinical study report).**

Table 11.4.1.6 Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Baseline-Corrected Cyanocobalamin-Informational

Parameter	Test A	Reference B	Ratio	CI	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	17788.15	14955.73	1.1894	0.8092 - 1.7483	82.5776
Cmax (pg/mL) (N=21)*	674.57	648.84	1.0397	0.8784 - 1.2305	32.3513

*N=Number of subjects with evaluable data for both the test and reference products.

Figure 14.2.3 Mean Plasma Concentration versus Time Plot (Linear): Baseline-Corrected Cyanocobalamin (Informational)



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/s/

SANDRA SUAREZ
10/25/2013

ANGELICA DORANTES
10/25/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 21642 S-020 (SDN 322 and 329)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DMP		
Applicant:	Par Pharmaceuticals, Inc.	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nascobal Nasal Spray	**Supervisor (acting):** Richard Lostritto, Ph.D	
Generic Name:	Cyanobalamin Nasal Spray	**Date Assigned:**	Aug 5, 2013
Indication:	Maintenance of normal hematologic status in pernicious anemia	**Date of Review:**	September 17, 2013
Formulation/strengths	Nasal Spray, 500 mcg/spray		
Route of Administration	Nasal		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Desired Completion Date**
Email-Correspondence Aug 5, 2013	Aug 5, 2013	Sep 17, 2013
Type of Submission:	Correspondence/Request for concurrence on proposed studies	
Type of Consult:	Biopharmaceutics data needed to support the proposed manufacturing changes	

REVIEW: Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B12) for administration as a spray to the nasal mucosa. Nascobal 500 mcg/spray, Nasal Spray was approved by the FDA on January 31, 2005, for the maintenance of normal hematologic status in pernicious anemia. Each bottle of Nascobal Nasal Spray contains 2.3 mL of a 500 mcg / 0.1 mL solution of cyanocobalamin (multi-dose bottle). The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly.

On March 12, 2013, the Applicant submitted a Post Approval Supplement (S-020) seeking approval of Nascobal® Nasal Spray in a unit-dose device. In support of this change, the Applicant included CMC information, in vitro BE data and the results of an in vivo bioequivalence study comparing the Unit- Dose Nasal Spray Delivery Device Containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.) to NASCOBAL® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray. The results of the in vivo BE study showed lack of bioequivalence (the 90% CI were out of the 80-125 goal post for AUCt (0.800-1.748) for the baseline-corrected cyanocobalamin data. The Applicant attributed the failed BE result to a large intra-subject variability, primarily due to the endogenous presence of cyanocobalamin. A CR letter was issued on July 12, 2013, for this supplement citing the following biopharmaceutics deficiency[1]:

> *"The justification provided to explain the failure of BE for the upper bound of the 90% CI for AUC(0-t) for the baseline corrected cyanocobalamin data is not acceptable. Based on the review of the baseline cyanocobalamin data provided for the 24 hours prior to the administration of the dose, the levels of endogenous cyanocobalamin do not have very high variability. To support and justify the failure of BE for corrected data, we recommend that you provide data to support the inherent variability of endogenous cynacobalamin, for example, basal cynacobalamin levels for 72 hours".*

[1] CMC and Biopharmaceutics review entered in DARRTS by Deepika Lakhani on 7/11/2013.

On Aug 5, 2013, an Email correspondence was submitted by the Applicant containing further explanation/justification for the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data based on additional analysis conducted (See Appendix for details on the report). The Applicant's conclusions from this analysis are as follows:

1. The method of baseline adjustment influences the value of AUC_{0-72} as a result of the high number of BLOQ values in pre-dose and post-dose concentrations, the high number of zero and negative baseline-corrected post-dose concentrations, and the high contribution of the baseline concentrations to AUC_{0-72}.
2. Adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio is likely more representative of the true AUC ratio because of the "noise" in the post-dose concentrations from 36 to 72 hours.
3. Estimations of λ_z and $AUC_{0-\infty}$ from baseline-corrected data are unreliable in more than 55% of the 42 data sets. Even for the reliable estimates of λ_z the estimated half lives are not the clinically relevant or physiologically effective disposition half life, as they would be too short (< 30 hours) to explain the expected drug accumulation over 4 weeks to steady state following once-weekly intra-nasal dosing of cyanocobalamin-containing nasal spray products.

The Email correspondence also contained a request for guidance on the following points of clarification to be discussed via teleconference with the FDA:

1. In study 11205509 the endogenous cyanocobalamin baseline was stable over the 24-hour pre-dose period in the two periods but high within-period variability for BLOQ imputations of 0 was demonstrated, which could have led to inaccurate estimation of each subject's mean pre-dose concentration that was used to correct the post-dose concentrations in each period.
2. Baseline-corrected AUC_{0-72} is not a reliable parameter to demonstrate bioequivalence in study 11205509 because of the "noise" in the post-dose concentrations from 36 to 72 hours.
3. The failure of study 11205509 to demonstrate bioequivalence for AUC_{0-72} is a direct consequence of the unreliability of the baseline correction procedure and is not a result of product (device) differences.
4. We propose that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to evaluate bioequivalence of cyanocobalamin-containing nasal spray products. Evaluation of $AUC_{0-\infty}$ is not appropriate.
5. For an LLOQ value of 200 pg/mL in future studies, an imputation value of 100 pg/mL (½LLOQ) has scientific rationale for minimizing the bias and within-period variability in the estimation of the mean pre-dose concentration for use in baseline adjustment of post-dose concentrations.
6. If baseline-adjusted AUC is a requirement for bioequivalence evaluation of cyanocobalamin-containing nasal spray products then Par proposes that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to demonstrate BE of this product.
7. If confidence limits around the test-to-reference ratio are required to be within 80-125% then Par proposes to repeat the study with a reference-replicated design to accommodate the high within-subject variability in AUC_{0-24} and AUC_{0-72} (> 50%) induced by the baseline adjustment. BLOQ values will be imputed as ½LLOQ and both the FDA and Par baseline correction procedures will be evaluated if the LLOQ of the assay remains at 200 pg/mL. Every effort will be made to lower the assay LLOQ from 200 pg/mL. Par believes that sampling over a 72-hour pre-dose period is not necessary to demonstrate the stability of basal cyanocobalamin levels as recommended by FDA, considering the stability of the baseline over 24 hours.

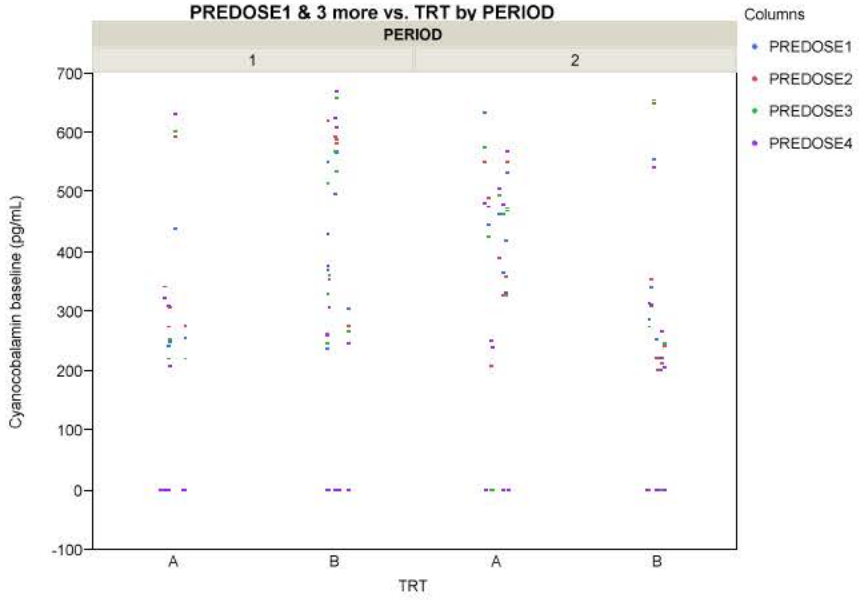
On the teleconference that took place on Aug 14, 2013, FDA seek further clarification on the BE study design and analytical methodology. FDA expressed their concerns on the sensitivity of the analytical

methodology as one of the sources of the BE failure. Par responded that the LLOQ could not be lowered because of the more stringent requirements for method validation compared to when the original assay with the lower LLOQ was conducted for the original application. The FDA viewed this teleconference as an opportunity for clarification and mentioned that feedback would be submitted on a later date following discussion with other disciplines.

This review summarizes the discussion/conclusions reached along with the input from several disciplines (OCP, Clinical and Biostatistics) on the document sent by the Applicant via Email on Aug 4, 2013.

Summary of the Discussions/Conclusions

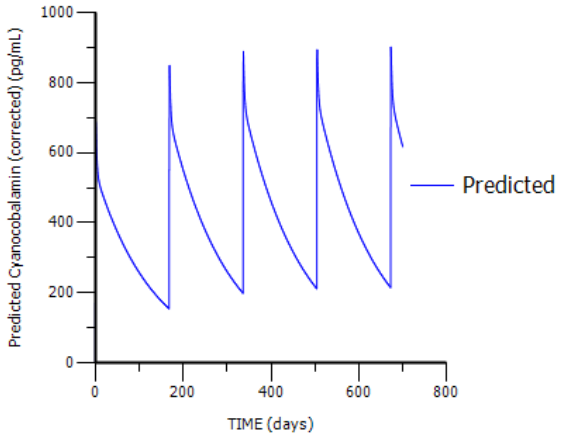
1. An internal statistical analysis showed that even when setting the BLOQ value to missing, BE in terms of AUC_{0-72} hours failed. The imputation method (e.g. BLOQ values being imputed as LLOQ, ½LLOQ, zero, missing, etc. influences the value of AUC; however, the outcome of the BE study corrected for baseline (failed BE), does not change for this particular drug product (Appendix, Table 4). This information along with the fact that the intra-subject mean baseline values were similar between periods (Figure 1), suggest that failing the BE study is likely due to a higher variability in drug delivery from the new proposed product. This is further supported by the fact that the BE analysis applied to baseline values (FDA internal analysis) showed BE among periods only when LLOQ was set to missing. However, as mentioned before, BE failed for baseline-corrected plasma levels independent of the method of imputation.



2. Given the nature of the plasma concentration-time profile following the nasal route of administration and the high variability in the observed plasma concentrations from 36 to 72 hour, AUC_{0-72} should be the PK metric use in the demonstration of bioequivalence in study 11205509, not AUC_{0-24} as proposed by the Applicant.
3. The use of adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be considered if the difference between them is less than 20%.
4. Given that the method of baseline adjustment (imputation approach) did not change the outcome of the BE results for this proposed product and it highly depends on the number of BLOQ values in pre-dose and post-dose concentrations, we cannot agree with the Applicant to

use imputation value of 100 pg/mL (½LLOQ). The Applicant should follow the FDA recommendations for baseline correction and imputation of negative values.

5. The use of baseline-adjusted PK data is highly recommended for bioequivalence evaluation of cyanocobalamin-containing nasal spray products, as it is for any other endogenously found drug substance.
6. We recommend the development of a more sensitive analytical method to decrease the bias due to the method of imputation implemented.
7. We consider that a difference of less than 20% (in the mean baseline-corrected AUC between both devices) is of no clinical relevance. This is justified by the conclusion made by the Clinical Reviewer[2] for the original submission of NDA 21642, who indicated that although Nascobal was shown not to be BE to the reference listed drug, the clinical use of this product requires the monitoring of patients to determine if adequate repletion of B12 has been achieved. Therefore, we consider that an additional BE study is not necessary, provided that the trough concentrations at steady state are above the abnormal levels (200 pg/mL)[3,4]. In order to make an estimation of the through concentrations at Steady State, computer simulations were ran internally using Phoenix Software following multiple dose (weekly) administrations of 500 mcg/spray to predict the Cmin and Cmax concentrations. The figure below shows that after multiple administrations the baseline-corrected cyanocobalamin Cmin is above 200 pg/mL for the new device. However, the Applicant will be requested to present additional data on the concentrations reached at Steady State.



RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed email communication received on August 5, 2013 under Supplement 20 (SDN 322 and 329) for NDA 21642 and has the following comments that should be conveyed to the Applicant.

COMMENTS TO BE CONVEYED TO THE APPLICANT:

1. Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the

recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:

a. Provide information/data (e.g. modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at Steady State are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite of its lower concentration-time profile pre and post administration.
c. A post-marketing commitment to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this Supplement.

2. We have the following advise/recommendations for the conduct of any future BE studies involving your cyanocobalamin nasal spray product:
   a. The imputation method (e.g. BLOQ values being imputed as LLOQ, ½LLOQ, zero, missing, etc.) influences the value of AUC; however, the outcome of the BE study corrected for baseline (namely failed BE) does not change for this particular drug product. This information along with the fact that the intra-subject mean baseline values were similar between periods, suggest that failing of the BE study is likely due to a higher variability in drug delivery from the new proposed product. This is further supported by the fact that BE analysis applied to baseline values (FDA internal analysis) showed BE among periods only when LLOQ was set to missing. However, as mentioned before, BE was failed for baseline-corrected plasma levels independent of the method of imputation.
   b. Given the nature of the plasma concentration-time profile following the nasal route of administration and the high variability in the observed plasma concentrations from 36 to 72 hour, AUC_{0-72} should be the PK metric use in the demonstration of bioequivalence for your proposed product.
   c. The use of adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be considered if the difference between them is less than 20%.
   d. Given that the method of baseline adjustment (imputation approach) did not change the outcome of the BE results for this proposed product and it highly depends on the number of BLOQ values in pre-dose and post-dose concentrations, we cannot agree with your proposal of using imputation value of 100 pg/mL (½LLOQ). Baseline correction should follow the FDA recommendations.
   e. The use of baseline-adjusted PK is highly recommended for bioequivalence evaluation of cyanocobalamin-containing nasal spray products, as it is for any other endogenously found drug substance.
   f. We recommend the development of a more sensitive analytical method for the quantification of cyanocobalamin in plasma in order to decrease the bias due to the method of imputation being implemented and increase on the accuracy of the results.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

c.c. RLostritto; DLakhani; IZadezensky; SChung

[2] Medical Review entered in DARRTS by Dr. Mary Parks on 10/19/04.
[3] Vitamin B12 levels (Online MedLine Plus http://www.nlm.nih.gov/medlineplus/ency/article/003705.htm)
[4] Email communication with Medical Reviewer, Dr. William Lubas.

APPENDIX (Document submitted on Aug 4, 2013 by the Applicant)

Par Pharmaceutical (Par's) Points of Discussion:

In Par's previous response dated June 28, 2013 we explained that the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data is a direct result of the high intra-subject variability for this parameter. We proposed that the high intra-subject variability is influenced by five factors:

1. The high baseline contribution of endogenous to total post-dose cyanocobalamin concentrations,
2. The lack of any measureable baseline concentrations in only one of the two periods for some subjects (# 2, 10 and 14),
3. The large number of below the LLOQ (BLOQ) values reported during the baseline period: 10 subjects (# 1, 2, 3, 7, 10, 14, 17, 20, 22 and 23) had four or more BLOQ values, out of a possible five pre-dose samples (-24, -18, -12, -6 and -1 hour), in at least one of the two periods,
4. The mixture of measureable pre-dose concentrations and at least one pre-dose concentration BLOQ for the five pre-dose samples in several (15 of 44) periods, and
5. The similarity in magnitude of the assay lower limit of quantitation (LLOQ = 200 pg/mL) to the baseline concentrations.

We postulated that the latter three factors largely contribute to inaccurate estimations of the mean of the five pre-dose concentrations that is used to correct the post-dose concentrations, and correspondingly likely lead to inaccurate adjustment in the baseline-corrected AUC_{0-t}.

We have conducted additional analyses of the data from study 11205509 to demonstrate that 1) the estimations of the mean baseline concentration are indeed variable within each period and between the subjects in the two periods, and 2) the adjusted BE results are highly dependent on the method of baseline correction. Our conclusion is that baseline-corrected AUC_{0-72} data are unreliable and the failure of the study is a direct consequence of the unreliability of the baseline correction procedure and is not a result of product (device) differences.

Comparison of cyanocobalamin baseline concentrations within and between periods in study 11205509

Raw data:
Tables 1 and 2 below show the mean cyanocobalamin baseline concentrations in periods 1 and 2 and their associated within-period and between-subject variability at each of the five pre-dose sampling times in the two periods. Three methods of imputation for the BLOQ value were evaluated because of the high number of pre-dose BLOQ values (90 of a total of 220 in the two periods).

1. Replace BLOQ with 0 (current FDA-recommended procedure)
2. Replace BLOQ with 100 (one-half the LLOQ value)
3. Replace BLOQ with 200 (LLOQ value)

Table 1. Mean cyanocobalamin baseline concentrations (pg/mL) in period 1 of study 11205509 and their associated within-period and between-subject variability (n = 22 subjects).

Period 1		**Time (hours) (n = 22 per time point)**					**Overall Mean (n = 5)**	**Pooled Intra %CV**
	BLOQ Imputation	**-24**	**-18**	**-12**	**-6**	**0**		
Mean	0	194.39	247.20	231.44	226.59	269.05	233.73	31.05
	100	244.39	288.11	272.35	272.05	296.32	274.64	19.95
	200	294.39	329.01	313.26	317.50	323.60	315.55	13.56
Inter %CV	0	113.65	96.58	99.92	108.27	87.92	101.27	
	100	72.12	67.97	69.83	74.62	69.70	70.85	
	200	46.27	47.82	49.38	52.15	56.58	50.44	

Table 2. Mean cyanocobalamin baseline concentrations (pg/mL) in period 2 of study 11205509 and their associated within-period and between-subject variability (n = 22 subjects).

Period 2		**Time (hours) (n = 22 per time point)**					**Overall Mean (n = 5)**	**Pooled Intra %CV**
	BLOQ Imputation	**-24**	**-18**	**-12**	**-6**	**0**		
Mean	0	215.49	225.84	202.73	235.80	242.54	224.48	37.37
	100	260.94	262.20	252.73	272.17	278.90	265.39	21.15
	200	306.39	298.56	302.73	308.53	315.27	306.30	11.60
Inter %CV	0	104.08	93.59	113.04	88.83	90.57	98.02	
	100	68.96	65.94	72.85	61.85	64.34	66.78	
	200	45.75	47.31	47.31	43.05	45.96	45.88	

The mean values for each of the five pre-dose concentrations within each period are similar in magnitude, regardless of the method of BLOQ imputation, indicating the baseline is stable with minimal circadian fluctuation, at least over the 24-hour pre-dose period, and that the subjects were well stabilized on the low vitamin B_{12} diet. The shape of the mean concentration-time profiles over the 24-hour pre-dose sampling period is similar between periods 1 and 2 (see **Figures 1 and 2**).

Figure 1. Mean cyanocobalamin baseline concentrations in period 1 of study 11205509.

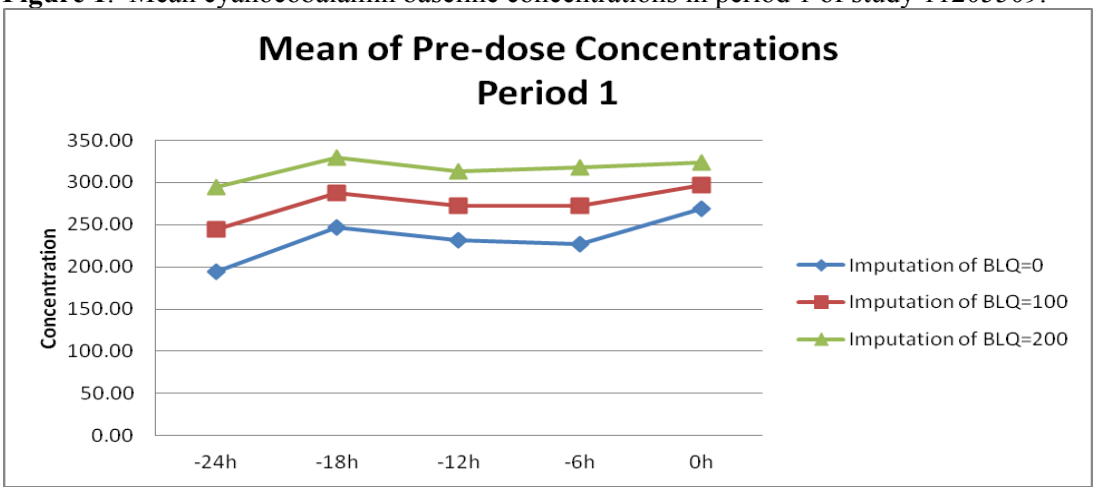
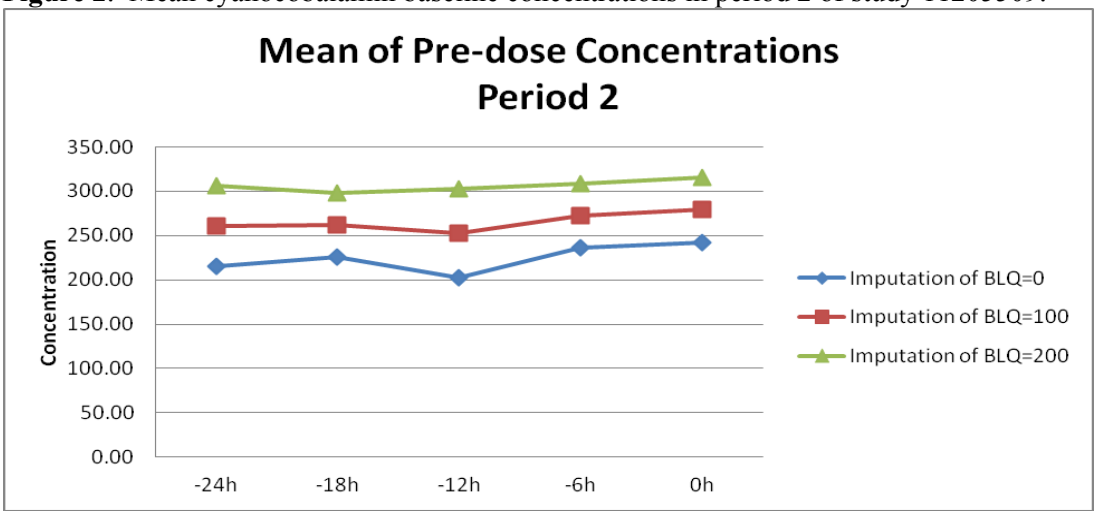


Figure 2. Mean cyanocobalamin baseline concentrations in period 2 of study 11205509.



However, the overall mean of the pre-dose concentrations, the within-period variability, and the between-subject variability at each of the five pre-dose sampling times are influenced by the imputation method. For example, the overall mean pre-dose concentration is lowest and the variabilities are highest when BLOQ values are replaced with 0, with inter-subject %CVs near 100% in each period and within-period %CVs of 31% for period 1 and 37% for period 2. Whereas the overall mean pre-dose concentration is highest and the variabilities are lowest when the BLOQ values are replaced with the LLOQ value of 200 pg/mL.

Ln-transformed data:
The pre-dose concentrations in periods 1 and 2 were also analyzed following ln-transformation of the data by a mixed model incorporating the fixed effects of period and time and random effect of subject. The BLOQ values could not be replaced with 0 so various imputations from the LLOQ value of 200 to one-eighth of the LLOQ (25 pg/mL) were assessed for the 21 subjects (subject # 20's data excluded). There was no period-by-time interaction for each of the different imputations. The results showed that the intra-subject variability, which is a measure of the consistency of the difference between the baseline concentrations at the different sampling times within a subject pooled over all subjects, increases from 16% to 94% as the imputation approaches 0, further

supporting that an imputation of 0 for BLOQ, as was done in the originally submitted data, magnifies variability (see **Table 3** below).

Table 3. Intra-subject variability of cyanocobalamin baseline concentrations for various imputations for BLOQ in study 11205509.

Imputation for BLOQ	Pooled Intra-subject %CV for pre-dose concentrations
LLOQ = 200	15.53
½LLOQ = 100	35.14
¼LLOQ = 50	61.31
⅛LLOQ = 25	93.88

Conclusions on baseline data in study 11205509

1. The different methods of imputation for BLOQ values (0, 100 and 200) give different overall mean pre-dose concentrations and within-period and between subject %CV values.
2. The high number of BLOQ values for the pre-dose concentrations leads to high within-period variability for the estimation of each subject's mean pre-dose concentration in the two periods when BLOQ is replaced with 0.
3. This high within-period variability for BLOQ imputations of 0 potentially led to inaccurate estimation of each subject's mean pre-dose concentration that was used to correct the post-dose concentrations in each period.

Baseline adjustment of post-dose concentrations in study 11205509

In the originally submitted data, the post-dose concentrations were adjusted for baseline by subtracting the mean of the five pre-dose concentrations (with imputation of 0 for BLOQ values) from the individual post-dose concentrations. The pre-dose concentration at time 0 was *a priori* set to the mean pre-dose value. Negative baseline-corrected values were set to 0 as recommended in FDA individual bioequivalence guidances. This method is hereinafter referred to as the FDA method. We performed additional analyses of the FDA method with imputation of 100 (½LLOQ) and 200 (LLOQ) for the pre-dose and post-dose BLOQ values. We also re-analyzed the AUC data using a different method of baseline adjustment by keeping the negative baseline-corrected values in the analysis. In this method, hereinafter referred to as the Par method, the pre-dose and post-dose BLOQ values were also imputed as 0, 100 or 200, as in the FDA method. We believe this is a more mathematically correct way to baseline adjust the data. Because concentrations approached the LLOQ after 24 hours in some subjects, AUC_{0-24}, in addition to AUC_{0-72} and C_{max}, was analyzed with unadjusted and baseline-adjusted data for both methods. Data from subject # 20 were excluded in all analyses because there was only one post-dose concentration in period 1. The results for the FDA and Par baseline-correction methods using the three different imputation methods are presented in **Table 4** below.

Table 4. Bioequivalence results for study 11205509 using the FDA and Par baseline correction methods and different imputation methods for BLOQ values.

Imputation	A/B ratio	90% lower CL	90% upper CL	Pooled intra-subject %CV
Ln(Cmax)				
Unadjusted	99.73	87.11	114.73	26.21
0 (FDA or Par)	103.97	87.84	123.05	32.35
100 (FDA or Par)	102.71	86.17	122.42	33.77
200 (FDA or Par)	99.19	80.75	121.84	39.98
Ln(AUC_{0-72})				
Unadjusted	105.90	92.08	121.79	26.63
0 (FDA)	118.94	80.91	174.83	82.58
100 (FDA)	119.42	82.35	173.17	78.89
200 (FDA)	119.14	81.39	174.42	81.46
0 (Par)	87.19	64.61	117.66	57.92
100 (Par)	90.69	69.44	118.43	50.53
200 (Par)	95.83	70.11	130.98	60.22
Ln(AUC_{0-24})				
Unadjusted	96.29	85.38	108.61	22.82
0 (FDA)	103.75	78.01	137.99	57.42
100 (FDA)	104.69	79.43	138.00	55.35
200 (FDA)	102.82	76.67	137.89	59.35
0 (Par)	103.79	77.04	139.83	60.42
100 (Par)	110.29	77.58	156.79	73.68
200 (Par)	92.50	70.17	121.93	53.94

Regardless of the baseline-correction and imputation methods the pooled intra-subject %CV values remain high at > 50% for the AUC parameters. However, the baseline-correction method has a large influence on the ratios and %CVs for AUC_{0-72}, with adjusted ratios closer to 100% and smaller %CVs for the Par method. The adjusted AUC_{0-24} ratios are closer to 100% than are the adjusted AUC_{0-72} ratios, particularly for the FDA method. There are larger differences in adjusted AUC_{0-24} ratios for the Par method depending on the imputation method. Though most concentration-time profiles show positive baseline-corrected values, all these differences in adjusted AUC ratios are a consequence of the comparatively high number of zero and negative baseline-corrected concentrations in the post-absorption phase (see **Table 5**), suggesting that baseline adjustment of AUC data is not recommended for study 11205509.

Table 5. Number of post-dose baseline-corrected values that result in 0 or negative values for various imputations for BLOQ in study 11205509.

Imputation for BLOQ	Number of 0 concentrations	Number of negative concentrations
LLOQ = 200	21	15
½LLOQ = 100	21	13
0	21	11

A listing of each subject's concentrations from -24 hours to 72 hours post-dose for unadjusted concentrations is in the 11205509_unadjusted.xpt SAS file. Excluding data from subject # 20 there are 25 post-dose BLOQ values from six subjects (# 2, 3 14, 17, 21 and 22). Most of the BLOQ values occur for subject # 17. Listings of the baseline-adjusted post-dose concentrations for the different imputation methods (0, 100, 200) are in the 11205509_0_adjusted.xpt, 11205509_100_adjusted.xpt, and 11205509_200_adjusted.xpt SAS files, respectively. The numbers of zero and negative concentrations that result from the baseline adjustment are shown in **Table 5** above (subject # 20 excluded). Most of the zero and negative concentrations are associated with subjects # 17 and 21, respectively. Zero concentration values result when both the mean pre-dose concentration and the post-dose concentration are BLOQ.

There is minimal decline in baseline-corrected concentration from 20 hours onwards, which suggests there is very slow release of vitamin B_{12} from tissues following administration and/or the estimated mean baseline concentration over the 24-hour period before dosing may not be a reflection of post-dose endogenous concentrations for accurate baseline correction of post-dose concentrations over the 72-hour sampling period. The latter is likely an inherent characteristic of vitamin B_{12} pharmacokinetics considering vitamin B_{12} undergoes entero-hepatic recycling.

Attempted estimations of terminal rate constant (λ_z), terminal half life ($t_{½,z}$), and $AUC_{0-\infty}$

In Par's previous response dated June 28, 2013, theoretical reasons were provided to justify not providing the requested baseline-corrected cyanocobalamin data for the $t_{½,z}$, λ_z and $AUC_{0-\infty}$ parameters. As part of the additional analyses of the data from study 11205509 we attempted to estimate the three parameters to further support those arguments. The data set with imputations of 0 for BLOQ values was used. At least three sampling times (not including Tmax) were included in the estimations of λ_z. The following criteria were used to determine if the estimate of λ_z was considered reliable:

1. The adjusted R^2 value from the linear regression is > 0.8, and
2. The associated $t_{½,z}$ is shorter than the time span over which λ_z is estimated, as proposed by Purvis (Method 1),[1] or
3. The associated $t_{½,z}$ is shorter than half of the total sampling interval or shorter than half of the time of last measureable concentration (t_{last}) if t_{last} is less than the time of last sample collection, as proposed by Colucci et al (Method 2).[2]

If λ_z was considered reliable then $t_{½,z}$ and $AUC_{0-\infty}$ were estimated. $AUC_{0-\infty}$ was considered reliable if the extrapolated portion from AUC_{0-t} was < 20%.

Using Method 1, 18 of 42 (43%) data sets have reliable λ_z estimates and using Method 2, 13 of 42 (31%) data sets have reliable λ_z estimates. The reliable estimates all have associated $t_{½,z}$ values that are < 30 hours. Of the 30 data sets with adjusted R^2 values of > 0.8, 25 have associated $t_{½,z}$ values of > 24 hours (i.e., long elimination half life, as defined in FDA's Draft Guidance on Amiodarone Hydrochloride, December 2010); most of these half lives are longer than the time span over which λ_z is estimated (Method 1) or longer than half of t_{last} (Method 2). This further supports that cyanobalamin has a long terminal half life such that truncation of AUC to 72 or 24 hours is warranted. Ten (10) of 42 data sets have reliable $AUC_{0-\infty}$ estimates and only two subjects (# 15 and 18) have reliable $AUC_{0-\infty}$ values in both periods.

These results strongly support that estimations of λ_z and $AUC_{0-\infty}$ parameters from baseline-adjusted data are not appropriate for cyanocobalamin in study 11205509, as originally proposed in Par's previous response.

Conclusions on baseline-correction in study 11205509

4. The method of baseline adjustment influences the value of AUC_{0-72} as a result of the high number of BLOQ values in pre-dose and post-dose concentrations, the high number of zero and negative baseline-corrected post-dose concentrations, and the high contribution of the baseline concentrations to AUC_{0-72}.
5. Adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio is likely more representative of the true AUC ratio because of the "noise" in the post-dose concentrations from 36 to 72 hours.
6. Estimations of λ_z and $AUC_{0-\infty}$ from baseline-corrected data are unreliable in more than 55% of the 42 data sets. Even for the reliable estimates of λ_z the estimated half lives are not the clinically relevant or physiologically effective disposition half life, as they would be too short (< 30 hours) to explain the expected drug accumulation over 4 weeks to steady state following once-weekly intra-nasal dosing of cyanocobalamin-containing nasal spray products.[3]

Overall Points of Clarification:

8. In study 11205509 the endogenous cyanocobalamin baseline was stable over the 24-hour pre-dose period in the two periods but high within-period variability for BLOQ imputations of 0 was demonstrated, which potentially could have led to inaccurate estimation of each subject's mean pre-dose concentration that was used to correct the post-dose concentrations in each period.
9. Baseline-corrected AUC_{0-72} is not a reliable parameter to demonstrate bioequivalence in study 11205509 because of the "noise" in the post-dose concentrations from 36 to 72 hours.
10. The failure of study 11205509 to demonstrate bioequivalence for AUC_{0-72} is a direct consequence of the unreliability of the baseline correction procedure and is not a result of product (device) differences.
11. We propose that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to evaluate bioequivalence of cyanocobalamin-containing nasal spray products. Evaluation of $AUC_{0-\infty}$ is not appropriate.
12. For an LLOQ value of 200 pg/mL in future studies, an imputation value of 100 pg/mL (½LLOQ) has scientific rationale for minimizing the bias and within-period variability in the estimation of the mean pre-dose concentration for use in baseline adjustment of post-dose concentrations.
13. If baseline-adjusted AUC is a requirement for bioequivalence evaluation of cyanocobalamin-containing nasal spray products then Par proposes that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to demonstrate bioequivalence of this product.
14. If confidence limits around the test-to-reference ratio are required to be within 80-125% then Par proposes to repeat the study with a reference-replicated design to accommodate the high within-subject variability in AUC_{0-24} and AUC_{0-72} (> 50%) induced by the baseline adjustment. BLOQ values will be imputed as ½LLOQ and both the FDA and Par baseline correction procedures will be evaluated if the LLOQ of the assay remains at 200 pg/mL. Every effort will be made to lower the assay

LLOQ from 200 pg/mL. Par believes that sampling over a 72-hour pre-dose period is not necessary to demonstrate the stability of basal cyanocobalamin levels as recommended by FDA, considering the stability of the baseline over 24 hours.

References

1. Purves RD. Bias and variance of extrapolated tails for area-under-the-curve (AUC) and area-under-the-moment-curve (AUMC). *J Pharmacokinet Biopharm.* 1992;20(5):501-510.
2. Colucci P, Turgeon J, Ducharme MP. How critical is the duration of the sampling scheme for the determination of half-life, characterization of exposure and assessment of bioequivalence. *J Pharm Pharmaceut Sci.* 2011;14(2):217-217.

Product Label for Nascobal® (Cyanocobalamin, USP) Nasal Spray, 500 mcg/spray. Par Pharmaceutical Companies, Inc. (Manufactured for Q

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

/s/

SANDRA SUAREZ
09/17/2013

ANGELICA DORANTES
09/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021642Orig1s020

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products (DMEP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 021642/S-020

Name of Drug: Nascobal (cyanocobalamin, USP) Nasal Spray, 500 mcg/spray

Applicant: Par Pharmaceutical, Inc.

Material Referenced:
Previously approved supplements:

- Approval letter and labeling for S-002 dated September 15, 2006
- Approval letter and labeling for S-015 dated December 8, 2011
- Approval letter and labeling for S-016 dated January 24, 2012

S-020:

- CMC review dated July 11, 2013
- Complete Response letter dated July 12, 2013
- DMEPA labeling review dated July 12, 2013
- RPM email to applicant on August 6, 2013 (DMEPA labeling revision requests)
- ONDQA Biopharmaceutics review dated September 17, 2013
- RPM email to applicant on September 20, 2013 (ONDQA Biopharmaceutics reviewer advice)
- ONDQA Biopharmaceutics review dated October 25, 2013
- RPM email to applicant on October 31, 2013 (ONDQA Biopharmaceutics reviewer advice)
- DMEPA labeling review dated December 11, 2013
- ONDQA Biopharmaceutics review dated January 30, 2014
- ONDQA Biopharmaceutics review addendum dated April 21, 2014
- RPM email to applicant on April 17, 2014 (carton/container revision request from CMC reviewer; DARRTS communication dated April 22, 2014)
- CMC review dated April 23, 2014
- Email chain between RPM and applicant (April 11-28, 2014) regarding final agreed-upon labeling discussion and agreement on April 25, 2014 (DARRTS communication dated June 6, 2014)

Labeling Reviewed

Submission Dates:
April 25, 2014 (Final Agreed-Upon Package Insert - Word format; Trade Carton Labels, Sample Carton Label – pdf format)

October 25, 2013 (Trade Blister Label, Sample Blister Label, Device Label – pdf format)

Receipt Dates:
April 25, 2014 (Final Agreed-Upon Package Insert - Word format; Trade Carton Labels, Sample Carton Label – pdf format)

October 25, 2013 (Trade Blister Label, Sample Blister Label, Device Label – pdf format)

Background and Summary Description:
On March 11, 2013, the applicant submitted this CMC supplement (with labeling), which proposed a new unit dose device to replace the currently approved packaging configuration of 1.3 mL in 3 mL multi-dose glass bottles. On July 12, 2013, a Complete Response (CR) letter issued. A series of communications between the applicant and FDA occurred over the August-October timeframe, including a teleconference on August 14, 2013, and follow-up written responses and clarification sent by FDA to the applicant via email on August 26, 2013, and again by FDA via email on October 30, 2013. (Refer to email chains in DARRTS dated September 20 and October 31, 2013.) On August 6, 2013, labeling comments and recommendations (from the DMEPA labeling review dated July 12, 2013) were conveyed to the applicant via email.

On October 25, 2013, the applicant submitted a Complete Response amendment (resubmission) to S-020. This resubmission included responses to ONDQA Biopharmaceutics deficiencies conveyed in the CR letter dated July 12, 2013, and revised labeling in response to the labeling comments sent via email on August 6, 2013. On November 14, 2013, the applicant submitted product samples in response to the request included in the same labeling comments email.

On December 9, 2013, the applicant submitted a revised package insert in Word format to S-020, in response to a request sent via email on November 21, 2013 (the resubmission dated October 25, 2013, did not include this, as the PI was submitted only in SPL and pdf formats).

On February 13, 2014, the applicant sent an email summarizing a recently discovered issue which required a revision to their finished product monograph, specifically the Net Content <755> test. A teleconference was held with the applicant and FDA (Jennifer Johnson of DMEP and Ramesh Raghavachari of ONDQA) to discuss this issue. An agreement was made to allow the applicant to submit an amendment (including summary and justification for the finished product specification change), which was intended to be designated as a major amendment and extend the sNDA review clock by two months. However, once the amendment was received, it was discovered after internal communication between staff in DMEP, the document room, the Data Quality Management Team (within the Office of Business Informatics), Performance Analysis and Data Services (within the Office of Program and Strategic Analysis), ODE-II and the OND Immediate Office that the regulations do not permit review clock extensions for CMC

manufacturing supplements beyond the first review cycle (and resubmitted manufacturing supplements are not subject to PDUFA regulations/performance goals).

On April 17, 2014, an email was sent to the applicant, requesting revisions to the carton labels included in the October 25, 2013, resubmission (refer to email communication in DARRTS dated April 22, 2014). (b) (4) The applicant submitted revised carton labels via email on April 22, 2014, which were reviewed by and deemed acceptable to CMC on April 23, 2014, and to DMEPA on April 24, 2014. This was communicated to the applicant via email on April 24, 2014, and on April 25th the final agreed upon labeling and labels were sent by FDA to the applicant via email. On that same day, the applicant submitted an official amendment to S-020, which contained the final agreed-upon package insert and revised carton labels. (Since there were no changes to the acceptable device and blister labels included in the October 25, 2013, resubmission, these were not included in the April 25th submission.)

Note: the ONDQA Biopharmaceutics review dated January 30, 2014, included a request for a postmarketing commitment (PMC) study; after an internal team meeting on April 21, 2014, it was determined that this PMC study would no longer be necessary. (Refer to ONDQA Biopharmaceutics review addendum dated April 21, 2014, and to the CMC review dated April 23, 2014.) This was conveyed to the applicant via email on April 21, 2014.

Review

Review of the Package Insert

The applicant's final agreed-upon package insert (submitted on April 25, 2014) is being compared to the currently approved package insert (approved with S-015 on December 8, 2011. Additions are denoted by underline and deletions are denoted by ~~strikethrough~~.

(b) (4)

9 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Review of the Carton and Container Labels

The applicant's final agreed upon carton and container labels (submitted to S-020 on October 25, 2013 and on April 25, 2014) are being compared to the currently approved carton and container labels (approved with S-015 on December 8, 2011, and with S-016 on January 24, 2012).

Trade Carton Labels (compared to carton label approved with S-015)

(b) (4)

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Note: the changes to the carton and container (trade and sample blister) labels are acceptable. Refer to DMEPA review dated December 11, 2013, and to CMC review dated April 23, 2014. DMEPA also indicated agreement to the revised carton labels via email on April 24, 2014.

Device Label
Note: there is no device label to which this label can be compared, given the provisions of this supplement. However, the DMEPA review dated December 11, 2013, states that this label is acceptable.

Recommendations

An approval letter should issue for this supplement.

Jennifer Johnson	June 3, 2014
Regulatory Project Manager	Date
Pamela Lucarelli	June 4, 2014
Chief, Project Management Staff	Date

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

/s/

JENNIFER L JOHNSON
06/06/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Memo

Date:	December 10, 2013
Reviewer:	Sarah K. Vee, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Nascobal (Cyanocobalamin, USP) Nasal Spray, 500 mcg/spray
Application Type/Number:	NDA 21642/S-020
Applicant/sponsor:	Par Pharmaceutical
OSE RCM #:	2013-2658

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the revised device container label, blister labeling, carton and insert labeling for Nascobal (cyanocobalamin, USP) Nasal Spray, NDA 21642/S-020, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 21642 for Nascobal (cyanocobalamin, USP) Nasal Spray was approved on January 31, 2005.

On March 8, 2013 the Applicant submitted a prior approval supplement (PAS) that provides for a new unit dose device. Upon approval this unit dose device will replace the current packaging configuration of 1.3 mL, once current inventory is depleted. The insert has been revised to modify the Dosage and Administration section, how supplied section, and pharmacist assembly instruction.

The PAS received a Complete Response (CR) on July 12, 2013 and the Applicant submitted a response to the CR on October 25, 2013, which included revised labeling.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 8, 2013 PAS CMC supplement.

- Active Ingredient: cyanocobalamin, USP
- Indications of Use: 1) maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement; 2) for dietary deficiency of vitamin B_{12} in strict vegetarians; 3) for malabsorption of vitamin B_{12} resulting from structural or functional damage to the stomach; 4) conditions which cause inadequate secretion of intrinsic factor; 5) competition for Vitamin B_{12} by intestinal parasites or bacteria; and 6) inadequate utilization of Vitamin $B_{12.}$
- Route of Administration: nasal spray
- Dosage Form: solution
- Strength: 500 mcg per spray
- Dose and Frequency: 1 spray in one nostril per week
- How Supplied:
  - Current: A nasal spray actuator with dust cover, a bottle of nasal spray solution in a carton.
  - Proposed: 4 unit dose nasal spray devices per carton.
- Storage: Protect from light. Keep covered in carton until ready to use. Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.
- Container and Closure System:

- Current: Nascobal is filled into 3 mL, [redacted] (b) (4) glass bottles and closed with [redacted] (b) (4) screw cap [redacted] (b) (4) [redacted]. Each bottle of Nascobal® Nasal Spray is supplied with a nasal spray pump that is affixed to the bottle by the pharmacist at the time it is dispensed to the patient.
- Proposed: The proposed unit dose system consists of [redacted] (b) (4) [redacted]

2 METHODS AND MATERIALS REVIEWED

We reviewed the revised Nascobal labels, labeling and prescribing information submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label (Appendix A)
- Blister Labeling (Appendix B)
- Carton Labeling (Appendix C)
- Insert Labeling submitted October 25, 2013 (no image)

3 CONCLUSIONS

DMEPA concludes that the revised label and labeling are acceptable and have no further comments.

4 RECOMMENDATIONS

Based on this review, DMEPA concludes that the proposed label and labeling are acceptable and have no further comments.

If you have further questions or need clarifications, please contact Terrolyn Thomas, project manager, at 301-796-3981.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SARAH K VEE
12/10/2013

YELENA L MASLOV
12/11/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 2, 2013
Reviewer:	Sarah K. Vee, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Nascobal (Cyanocobalamin, USP) Nasal Spray, 500 mcg/spray
Application Type/Number:	NDA 21642/S-020
Applicant/sponsor:	Par Pharmaceutical
OSE RCM #:	2013-1352

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed device container label, blister labeling, carton and insert labeling for Nascobal (cyanocobalamin, USP) Nasal Spray, NDA 21642, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 21642 for Nascobal (cyanocobalamin, USP) Nasal Spray was approved on January 31, 2005.

On March 8, 2013 the Applicant submitted a prior approval supplement (PAS) that provides for a new unit dose device. Upon approval this unit dose device will replace the current packaging configuration of 1.3 mL, once current inventory is depleted. The insert has been revised to modify the Dosage and Administration section, how supplied section, and pharmacist assembly instruction.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 8, 2013 PAS CMC supplement.

- Active Ingredient: cyanocobalamin, USP
- Indications of Use: 1) maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement; 2) for dietary deficiency of vitamin B_{12} in strict vegetarians; 3) for malabsorption of vitamin B_{12} resulting from structural or functional damage to the stomach; 4) conditions which cause inadequate secretion of intrinsic factor; 5) competition for Vitamin B_{12} by intestinal parasites or bacteria; and 6) inadequate utilization of Vitamin B_{12}.
- Route of Administration: nasal spray
- Dosage Form: solution
- Strength: 500 mcg per spray
- Dose and Frequency: 1 spray in one nostril per week
- How Supplied:
  - Current: A nasal spray actuator with dust cover, a bottle of nasal spray solution in a carton.
  - Proposed: 4 unit dose nasal spray devices per carton.
- Storage: Protect from light. Keep covered in carton until ready to use. Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.
- Container and Closure System:
  - Current: Nascobal is filled into 3 mL, [redacted] (b) (4) glass bottles and closed with [redacted] (b) (4) screw cap [redacted] (b) (4). Each

bottle of Nascobal® Nasal Spray is supplied with a nasal spray pump that is affixed to the bottle by the pharmacist at the time it is dispensed to the patient.

- Proposed: The proposed unit dose system consists of (b) (4) [redacted].

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Nascobal medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the Nascobal labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	November 1, 2011 (date of last search) to June 11, 2013
Drug Names	cyanocobalamin (active ingredient) Nascobal (trade name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database searches identified five cases, respectively. Each case was reviewed for relevancy and duplication. After individual review, all five cases were not included in the final analysis because no medication errors were identified that involved Nascobal.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on June 18, 2013 for additional cases and actions concerning Nascobal but did not identify any additional cases.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following submitted on March 8, 2013:

- Device Container Label (Appendix B)
- Blister Labeling 2013 (Appendix C)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton Labeling (Appendix D)
- Professional Sample Blister Labeling (Appendix E)
- Professional Sample Carton Labeling (Appendix F)
- Insert Labeling submitted March 8, 2013 (no image)

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Nascobal in OSE Review #2011-2277 and #2011-2604 dated November 10, 2011 and we evaluated the reviews to ensure all our recommendations were implemented.

3 DISCUSSION

The Applicant is proposing to replace the current device which consists of a 3 mL glass bottle supplied with a nasal spray pump that is affixed to the bottle (Appendix G) with a unit dose device (Appendix H). The current system requires the pharmacist to attach the actuator to the bottle at the time it is dispensed to the patient. The current design requires the patient to prime the spray bottle before each use. Since the bottle contains four doses of the medication, the patient is required to store the device in an upright position in a controlled environment (b) (4)

The proposed unit dose device will not require pharmacist manipulation prior to dispensing, each unit is packaged in a blister and it will not require priming. The new design requires minimizes the steps prior to using the device and the device can be discarded after each use.

We considered whether human factors usability study is needed due to the change of the device and concluded that the usability study is not needed since it functions as any other commonly available nasal spray device that is on the market and ready to use (e.g. saline nasal sprays, common cold nasal spray products, fluticasone nasal spray, etc.). The design and use of this nasal spray does not introduce any new or unique aspects that the layperson would have difficulty using. Thus, we do not have any objections for the proposed device design change and only have recommendations for labels and labeling which need improvements.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label and labeling to promote the safe use of the product.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

A. Container Label

1. (b) (4)

2. Revise and relocate the strength of the product, ("500 mcg/spray" or "500 mcg per spray"), to appear below the proprietary and established names.

3. If space permits, incorporate the net quantity statement to read "1 spray" or "1 spray per device".

4. Ensure the first 10 characters of the linear bar code represent the National Drug Code as per 21 CFR 207.35.

B. Blister Labeling (Trade and Professional Sample)

1. Each blister should contain the expiration date and lot number per 21 CFR 201.17.

2. Relocate the strength statement to appear on a separate line of text directly below the established name.

3. Relocate the route of administration statement "For nasal use only" to appear directly below the strength statement.

4. The spray bottle that this single dose device is replacing required priming before each dose, thus the patient may attempt to "prime" this new device before use leading to drug loss and under dosing errors. As a result, we recommend the statement (b) (4) be revised to read "Do not prime before use" since the previous labeling referred to "priming" the device (b) (4)

5. Consider increasing the prominence of the statement "1 spray per device" and "Do not prime before use."

C. Carton Labeling (Trade and Professional Sample)

1. See recommendation A.2.

2. We recommend that the patient instructions for use be retained on the side panel. Although the package insert is included in the carton, it may be separated from the packaging and having the instructions for use on the carton would provide an alternate place the patient can refer to how to use the device.

3. Revise the established name (i.e., active ingredient and dosage form) to appear with equal prominence similar to the proposed presentation on the container label.

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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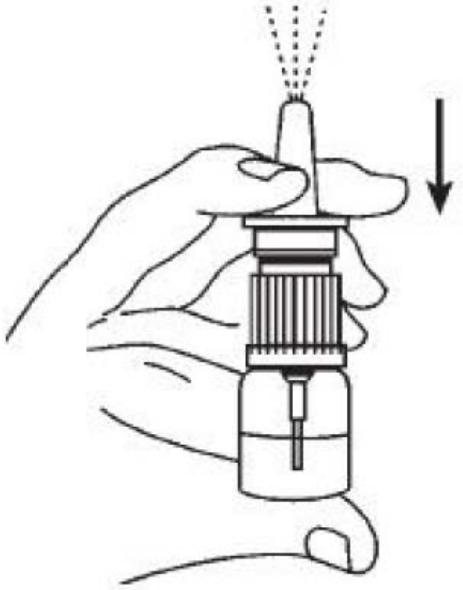
Appendix G: Current Device



Appendix H: Proposed Device

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/s/

YELENA L MASLOV on behalf of SARAH K VEE
07/12/2013

YELENA L MASLOV
07/12/2013

SCOTT M DALLAS
07/12/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021642Orig1s020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Selby, Meredith
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)
Date: Monday, April 28, 2014 3:37:52 PM

Hi Jennifer,

We did not resubmit the device and blister labels, as they are unchanged from what was last submitted in our 10/25/2013 submission (Sequence 0015 - Response to the FDA Complete Response Letter dated July 12, 2013). Do you have any idea when we can expect the Action Letter? Thank you.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Monday, April 28, 2014 3:22 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Hi Meredith,

Thank you for the update. We received your labeling amendment submitted on 4/25/14. Please note that since the container labels (device label and blister labels) were not included in the final labeling amendment we will include our standard request for submission of final carton/container labels in the action letter.

I will let you know if I have any questions as we wrap up this supplement.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Friday, April 25, 2014 2:32 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Hi Jennifer – I just wanted to let you know that we submitted a labeling amendment today with the requested changes to the package insert and carton labeling. We also included the updated SPL labeling. Please let me know if you have any questions, or if have any idea as to when we could expect approval. Thank you so much and have a great weekend!

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, April 24, 2014 5:24 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Thank you, Meredith. You are correct, we do not have any further comments/edits to the Nascobal PI.
The revised carton labels are also acceptable to our CMC and DMEPA reviewers.

Please respond via email regarding agreement/disagreement with the FDA revisions to the PI prior to sending a labeling amendment to S-020.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Thursday, April 24, 2014 5:12 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Thanks Jennifer. We are working on the update now and will send the amendment with the

Email chain between FDA (Jennifer Johnson) and applicant (Meredith Selby of Par Pharmaceutical Companies, Inc.) spanning the period April 11-28, 2014, regarding NDA 021642/S-020: includes agreement, explanations, and clarifications regarding the package insert and carton and container labels (and revision requests from FDA and acceptable responses from applicant). Also includes documentation that a post-marketing commitment (PMC) study is no longer needed as a condition of approval for this supplement.

From: Selby, Meredith
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert) - *Final agreed-upon labels and labeling*
Date: Monday, April 28, 2014 9:06:17 AM

Hi Jennifer,

Please note, we did update the revision number at the bottom of the revised PI to indicate "-05" from "-04" in our submitted final print label. That is the only change. Regarding the NDC numbers, the "-52' at the end of the NDC number designates the number of units. Since the device, each blister, and the sample carton all include one device, "-52" is designated. The "-82" is only for the trade carton, as 4 individual devices are included in the trade carton. The individual device, each blister, and the sample carton only include one device, therefore the unit number is "-52". Please let me know if you have any further questions.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Friday, April 25, 2014 3:40 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert) - *Final agreed-upon labels and labeling*

Hi Meredith,

Thank you for confirming agreement with the FDA edits to the package insert, as well as addressing my questions about the inadvertently omitted items from the PI approved with S-015. It appears that final SPL was never submitted following approval of S-015 on 12/8/11, so we appreciate the clarification.

We have no further comments; any other concerns/changes will be addressed in the (b) (4)

Therefore, I am attaching the final agreed-upon labeling to be attached to the action letter for S-020.

I am attaching the most recently revised carton and container labels as well, but have a couple questions prior to committing to final agreement. I see that the container labels (device, sample blister, trade blister) submitted with the resubmission on 10/25/13 all have the following NDC number listed: 49884-270-52 (whether or not the label is designated for the sample or trade product). However, on the carton labels, the trade NDC number ends in 270-82 and the sample NDC number ends in 270-52. Shouldn't the container trade/sample NDC numbers correspond to those on the carton labels? And how about the device label? What was the intended NDC code for

that?

Let me know if you have any further questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Thursday, April 24, 2014 5:34 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Hi Jennifer,

Sorry, I meant for confirmation that these are the only remaining comments to S-020, or will we be receiving another CR letter? I intend to submit these revisions in a formal amendment tomorrow, and want to make sure this is acceptable. Regarding the comments to the PI, we are in agreement with your edits.

To answer your questions regarding the asterisk in the Table, and the "Generalized" adverse reactions reported with parenteral Vitamin B12, these items should be in PI. They have always been in the PI and were in the final package insert labeling submitted in S-015, but were inadvertently omitted in the included SPL labeling. I hope this answers your questions. I can also include this explanation in the formal amendment if you would like.

Thank you for your help.

Best regards,
Meredith

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Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, April 24, 2014 5:24 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Thank you, Meredith. You are correct, we do not have any further comments/edits to the Nascobal PI.
The revised carton labels are also acceptable to our CMC and DMEPA reviewers.

Please respond via email regarding agreement/disagreement with the FDA revisions to the PI prior to sending a labeling amendment to S-020.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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Phone: (301) 796-2194
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jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Thursday, April 24, 2014 5:12 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Thanks Jennifer. We are working on the update now and will send the amendment with the revised PI and carton labeling tomorrow. I assume these are the only FDA comments to the S-020? Thanks.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, April 24, 2014 4:33 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020 (FDA-revised package insert)

Hi Meredith,

Please find attached the PI with our edits and comments, and let me know if you have any questions.

Kind Regards,

Jennifer

Jennifer Johnson
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Division of Metabolism and Endocrinology Products
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jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Thursday, April 24, 2014 12:25 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020

Hi Jennifer – Any update on the PI and when we will be receiving comments?

Thanks,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
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www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, April 22, 2014 6:43 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020

Hi Meredith,

Thank you for sending the revised carton labels so promptly. I will get back to you soon to confirm if they are acceptable for a final agreed-upon formal submission.

I will get back to you regarding the PI tomorrow.

Kind Regards,
Jennifer

Jennifer Johnson
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Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Tuesday, April 22, 2014 4:29 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020

Hi Jennifer,

As you recommended, I am sending you the carton revisions. Attached is the carton labeling with the requested revision (b) (4) Please let me know if these are acceptable. The only changes are (b) (4) and the relocation of the statement (or just a line space between) "One spray per device" to be separated from the ingredients. If they are acceptable, I will include in a formal submission, along with the package insert.

When can I expect the comments to the package insert? Do you still plan to send today?

Best regards,
Meredith

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www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Monday, April 21, 2014 3:41 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020

Hi Meredith,

Thank you for the update, and for the clarification regarding the missing paragraph from the S-015 approved labeling (SPL).

We held a team meeting this morning, and determined that a postmarketing commitment (PMC) study is not necessary at this time. I discussed your update with my CMC reviewers as well. We will need for revised carton labels to be submitted and reviewed prior to approval, (b) (4) However, you may submit the revised color mock-up carton labels to me via email prior to submission to the NDA supplement 020.

I will send to you the PI with our revisions and comments tomorrow.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Friday, April 18, 2014 2:55 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/ S-020

Hi Jennifer,

We are in the process of making the revisions to the carton labels, and will also make the revisions to the package insert as soon as we receive them from you. As we discussed yesterday, we will submit the revised labeling to the NDA (b) (4) [redacted]

Also as discussed yesterday, I wanted to clarify the situation regarding the paragraph from the PI that you describe below and the labeling approved with S-015. When Kati first brought this to my attention, I researched and was confused as all the draft and final print labeling submitted with S-011, S-015, (b) (4) and S-020 includes the paragraph, as it should definitely be there. The only place I found that it was missing was in the SPL submitted with S-015 and the corresponding "approved" labeling that was attached to the FDA approval letter for S-015. It should be there and it is, and always has been, in the PI with our marketed product. So I am hopeful that this will not hold up this supplement, as the labeling submitted with this supplement (S-020) is correct.

I await the comments to the PI and any other updates you have regarding the PMC. We will turn everything around as quickly as possible in order to hopefully receive approval on 4/25. Thank you for your help and have a great weekend!

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Thursday, April 17, 2014 4:44 PM
To: Selby, Meredith
Subject: RE: NDA 21-642/ S-020

Hi Meredith,

I also received your voicemail. Thank you for checking in again. I apologize for the extended delayed response, as I've/we've been swamped with numerous project priorities, including this one.

I have been discussing the remaining review items for S-020 with my team – here is the latest update:

- We will meet next Monday 4/21 to discuss the post-marketing commitment discussed previously (decision that we still want to require the PMC, and if so, the remaining necessary steps). I will update you after that meeting.
- We are wrapping up the CMC review of the supplement, including your amendment submitted on February 20th following the t-con we held with Dr. Ramesh Raghavachari. We do not have any issues with the submission; (b) (4) I will send a separate email to this effect shortly.

Regarding your question concerning the relevance of the labeling submitted to S-011 to that submitted to S-020, I understand the confusion given that the S-011 supplement/label provides for a different fill size. There is one paragraph that is relevant to both, however. The following paragraph (3rd to last paragraph in the Indications and Usage section) is included in the label contained in the resubmission to S-011 dated March 18, 2014, as well as in the label submitted to S-020 on December 9, 2013 (and in the label approved with S-002 on September 15, 2006) :

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 non-tropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B_{12}.

However, it is not included in the most currently approved label (package insert approved with S-015, approved on December 8, 2011). I assume that this was just an oversight at the time of submission/approval of S-015, but it is relevant because we conduct our labeling reviews using the currently approved label and compare it to the most recent proposed draft labeling.

I plan on sending labeling comments to you tomorrow, after clearance through my team leader.

th

We are still attempting to make the April 25 goal date if possible.

I hope this makes sense. If not, I am happy to discuss this further over the phone if you'd like.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Thursday, April 17, 2014 3:32 PM
To: Johnson, Jennifer
Subject: FW: NDA 21-642/ S-020

Hi Jennifer – I left you a voicemail message, but emailing you as well. Just wondering if you have any update regarding my questions from last week? We are only a week away from 4/25 and I am still hoping FDA will take action by then, but have not yet received labeling comments. Any update is appreciated. Thank you.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Selby, Meredith
Sent: Friday, April 11, 2014 4:46 PM
To: 'Johnson, Jennifer'
Cc: Lucarelli, Pamela K
Subject: RE: NDA 21-642/ S-020

Hi Jennifer,

Thank you for the response. Can you give me any expected timeframes for resolution of these items? I thought the labeling review was wrapping up and we would be receiving the comments a few weeks ago. Will we definitely be receiving labeling comments in advance of the 04/25 date in order to turn around and still meet the 4/25 action date? Can you confirm if you are working towards approval (aside from the labeling)? Or do you expect the action on 4/25 may be other deficiencies? We just need to know if we should continue to work towards launching on or about

4/25.

Also, I have been working with Kati to resolve the issues regarding S-011, but I am not clear why resolution of that labeling has any bearing on approval of this supplement. S-011 has been pending review at FDA since 4/20/2010, and is for a fill size (b) (4).

I apologize for so many questions, but I am getting these questions on a daily basis from my management and we are just trying to understand our timelines. Can you let me know when I should follow up with you again.

As always, thank you for your help.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Friday, April 11, 2014 2:17 PM
To: Selby, Meredith
Cc: Lucarelli, Pamela K
Subject: RE: NDA 21-642/ S-020

Dear Meredith,

Thank you for checking in again, and for your patience. I apologize for the delay, as I have been managing multiple issues for a variety of products recently. However, I have not forgotten about pending S-020, and we are working on tying up the remaining loose ends for this supplement.

At this point, these are the items for which I am working to achieve resolution:

- Status of CMC review (including the amendment received on 2/20/14, which I previously explained could not be used to extend the review clock as originally planned, per the current regulations)
- Status of decision regarding the post-marketing commitment clinical study proposed by ONDQA biopharmaceutics reviewers
- Discussion of package insert labeling with my review team
- Resolution of package insert labeling for S-011 (per resubmission received on 3/18/14), which I have been discussing with my colleague Kati Johnson

I will be in touch with you soon about these pending items.

Kind Regards,
Jennifer

Jennifer Johnson

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/s/

JENNIFER L JOHNSON

06/06/2014

Email discussion chain (4/11/14-4/28/14) between RPM and applicant regarding final agreed upon labeling negotiations for the PI and carton/container labels, and PMC study no longer being required as a condition of approval of S-020.

From:	Johnson, Jennifer
To:	Selby, Meredith (Meredith.Selby@parpharm.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 21642/S-020 (Nascobal Nasal Spray): Carton label revision request
Date:	Thursday, April 17, 2014 4:44:00 PM
Attachments:	sample-carton-label.pdf trade-carton-label- (b) (4) trade-carton-label- (b) (4)

Dear Meredith,

As we have been wrapping up the review of NDA 21642/S-020 (new unit dose device), we have discovered that your most recently submitted carton labels (submission dated October 25, 2013) (b) (4) Refer to the attached labels from your October 25, 2013, submission.

Please submit revised carton labels (b) (4) at your earliest convenience.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JENNIFER L JOHNSON
04/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Margarita Tossa, Safety RPM, OSE, (301) 796-4053**
Mail: OSE

FROM: **Jennifer Johnson, RPM, DMEP, (301) 796-2194**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 14, 2013	**N/A**	**21642/S-020**	**CMC supplement resubmission with labeling (OND-managed)**	**October 25, 2013**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nascobal (cyanocobalamin, USP) Nasal Spray, 500 mcg/spray	**Standard**	**Vitamin (other than D)**	**February 3, 2014**

NAME OF FIRM: **Par Pharmaceutical, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- **X** LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the revised labels and labeling for this CMC supplement resubmission received on October 25, 2013. Refer to the Complete Response letter and DMEPA labeling review dated July 12, 2013. The DMEPA labeling comments and a request for product samples were sent to the applicant via email on August 6, 2013. The revised labels and labeling are available via the following EDR link: \\CDSESUB1\evsprod\NDA021642\0015

Note: I am requesting that the applicant also submit a Word version of the package insert. The action goal date for this supplement is February 25, 2014. The review team for this supplement includes: Bill Lubas (clinical), CMC (Ramesh Raghavachari) and ONDQA Biopharmaceutics (Sandra Suarez).

Feel free to contact me with any questions.

Many thanks,
Jennifer

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply)
Jennifer Johnson	**X** DARRTS/EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

JENNIFER L JOHNSON
11/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021642/S-020

COMPLETE RESPONSE –CMC

Par Pharmaceutical Inc.
Attention: Meredith Selby
Director, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Selby:

Please refer to your Supplemental New Drug Application (sNDA) dated March 11, 2013, received March 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nascobal (cyanocobalamin, USP) Nasal Spray, 500 mcg/spray.

We also refer to your resubmission, dated and received October 25, 2013, to your supplemental new drug application.

This resubmission constitutes a complete response to our July 12, 2013, action letter. The user fee goal date is **February 25, 2014**.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER L JOHNSON
11/13/2013

From:	Johnson, Jennifer
To:	"Selby, Meredith"
Bcc:	Johnson, Jennifer
Subject:	RE: NDA 21-642/S-020 T-con (8/14/2013) - *FDA follow-up responses and decision regarding BE study*
Date:	Wednesday, October 30, 2013 7:33:00 PM
Attachments:	Clarification of FDA comments 1a-b Rev 1.doc

Hi Meredith,

Although we note that you submitted on October 25th your Complete Response to the CR letter which issued on July 12, 2013, we did recently complete review of your questions/clarification requests attached to your October 1st email (attached again to this email for your reference).

Our responses to those are as follows:

1. Does the Agency concur with the above approach to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency?

   FDA Response: ***Given the constraints in obtaining a reliable half-life following single administration of the product and the uncertainty in terms of whether after nasal administration the cyanocobalamin plasma concentrations are the result of nasal absorption only or both nasal and GI absorption which may be different in the patient population versus healthy volunteers we request that you provide the following information under a post-marketing commitment:***

   a. Report the baseline and steady state concentrations after one month of multiple dosing of cyancobalamin in a representative number of patients with chronic vitamin B12 deficiency receiving the new drug product, Nascobal Nasal Spray in a unit-dose device.

2. Par requests clarification if the Agency is requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 hr) geometric T/R ratio for unadjusted concentration data, as determined from the analysis of variance (Table 11.4.1.3 in the clinical study report),** is higher **at 1.0590**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.1 in the clinical study report).** Or is the Agency requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 hr) geometric T/R ratio for baseline-corrected concentration data, as determined from the analysis of variance (Table 11.4.1.6 in the clinical study report),** is higher **at 1.1894**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.3 in the clinical study report).**

   FDA Response: ***Explain why the AUC_t after the administration of the test (31164.66 pg/h/mL) is higher than the reference (29428.96 pg/h/mL), when the profile in Figure 14.2.1 for the test is lower than that for the reference.***

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Tuesday, October 01, 2013 4:06 PM
To: Johnson, Jennifer
Subject: RE: NDA 21-642/S-020 T-con (8/14/2013) - *FDA follow-up responses and decision regarding BE study*

Hi Jennifer,

After a careful review and internal discussion of the items in your email below, our team does have a few questions/clarifications regarding the FDA's requests. They are summarized in the attached document. Hopefully they are straightforward enough to respond to, but if you feel a quick T-con would be beneficial, we can certainly arrange that. Please advise once your team has had time to review. Once again, thank you for time and consideration regarding this submission.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
www.parpharm.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Friday, September 20, 2013 12:08 PM
To: Selby, Meredith
Subject: NDA 21-642/S-020 T-con (8/14/2013) - *FDA follow-up responses and decision regarding BE study*

Dear Meredith,

Thank you again for the teleconference discussion on August 14th and the follow-up written responses and clarification sent on August 26th. We have discussed your responses internally and have the following decision and comments to convey:

1. Upon further consideration, we believe that a difference of less than 20% in the mean

baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:

a. Provide information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at steady state are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite its lower concentration-time profile pre- and post-administration.
c. A post-marketing commitment study to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this supplement.

2. We have the following advice/recommendations for the conduct of any future BE studies involving your cyanocobalamin nasal spray product:

a. The imputation method (e.g., BLOQ values being imputed as LLOQ, ½LLOQ, zero, missing, etc.) influences the value of AUC; however, the outcome of the BE study corrected for baseline (namely failed BE) does not change for this particular drug product. This information, along with the fact that the intra-subject mean baseline values were similar between periods, suggest that failing of the BE study is likely due to a higher variability in drug delivery from the new proposed product. This is further supported by the fact that BE analysis applied to baseline values (FDA internal analysis) showed BE among periods only when LLOQ was set to missing. However, as mentioned before, BE failed for baseline-corrected plasma levels independent of the method of imputation.
b. Given the nature of the plasma concentration-time profile following the nasal route of administration and the high variability in the observed plasma concentrations from 36 to 72 hours, AUC_{0-72} should be the PK metric used in the demonstration of bioequivalence for your proposed product.
c. The use of adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be considered if the difference between them is less than 20%.
d. Given that the method of baseline adjustment (imputation approach) did not change the outcome of the BE results for this proposed product and it highly depends on the number of BLOQ values in pre-dose and post-dose concentrations, we cannot agree with your proposal of using the imputation value of 100 pg/mL (½LLOQ). Baseline correction should follow the FDA recommendations.
e. The use of baseline-adjusted PK is highly recommended for bioequivalence evaluation of cyanocobalamin-containing nasal spray products, as it is for any other endogenously found drug substance.
f. We recommend the development of a more sensitive analytical method for the quantification of cyanocobalamin in plasma in order to decrease the bias due to the method of imputation being implemented and to increase on the accuracy of the results.

Let me know if you have any questions after reviewing the above.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
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jennifer.johnson@fda.hhs.gov

From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Monday, August 26, 2013 3:30 PM
To: Johnson, Jennifer
Subject: NDA 21-642/S-020 T-con (8/14/2013)

Hi Jennifer,

This is just a follow up to our August 14, 2013 T-con with Par and the FDA to discuss the Biopharmaceutics review. During the t-con, Par suggested we follow up with written responses to the questions raised and answered during the t-con. These are included in the attached minutes from the t-con. I am also including a revised document "Par's Discussion Points for study 11205509, Amendment 1" which was previously sent to you by email on 8/5/2013 including a few clarifications based on the t-con. The revised document contains a few minor clarifications as well as an additional paragraph. The revisions are highlighted within the document. Hopefully these will facilitate Dr. Sharp's decision regarding our current Bioequivalence study. We look forward to hearing back from you in the next 1-2 weeks on the discussions at FDA and your decision regarding our current BE study and/or the need for a new study. As previously mentioned, the SAS files are available if requested. Thank you.

Best regards,
Meredith

Meredith Selby | Director, Regulatory Affairs
Par Pharmaceutical Companies, Inc. | One Ram Ridge Rd | Spring Valley, NY 10977
Phone: 845.573.5515 | Fax: 845.573.5795 | Meredith.Selby@parpharm.com
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1. **Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:**
   a. **Provide information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at steady state are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.**

Therapeutic drug monitoring for patients with vitamin B_{12} deficiency, as recommended in the Nascobal® product label, are based on actual observed blood concentrations of cyanocobalamin. Therefore, Par requests clarification if the Agency is requesting provision of information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the **baseline-unadjusted** cyanocobalamin **trough** concentrations are above 200 pg/mL **in patients with a vitamin B_{12} deficiency following multiple-dose administration of the test unit-dose nasal spray delivery device containing Nascobal® (Cyanocobalamin, USP) 500 mcg/Actuation Nasal Spray (Par Pharmaceutical, Inc.)**? The single-dose study (in the Summary Basis for Approval of Nascobal® NDA-21-642) and Par's single-dose study 11205509 were conducted in healthy volunteers. Therefore, if the Agency concurs with the above, Par proposes to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency. Because the average baseline cyanocobalamin concentrations are > 200 pg/mL in the healthy volunteers who participated in study 11205509 (i.e., 234 pg/mL in period 1 and 224 pg/mL in period 2 using 0 as the imputation for BLOQ values), both baseline-corrected and baseline-uncorrected data will be modeled.

A reliable estimate of the clinically relevant terminal elimination half life ($t_{½,z}$) is required to predict steady-state concentrations from single-dose data. However, the $t_{½,z}$ values estimated in study 11205509 were deemed unreliable for most data sets, as explained in the correspondence emailed to FDA on August 26, 2013 (Par's Discussion Points for study 11205509, Amendment 1). In study 11205509 the reliable estimates all have associated $t_{½,z}$ values that are < 30 hours, but these values are likely underestimated because of the short sampling duration (72 hr) relative to the 7-day dosing period. In Par's previous correspondence dated June 28, 2013, we estimated the clinically relevant half-life as 7 days from the 4-week multiple-dose Nascobal® nasal gel data presented as a graph in the product label. We propose to use a 7-day half-life for the modeling of the single-dose data.

Does the Agency concur with the above approach to model the single-dose data from study 11205509 in healthy volunteers to predict the baseline-unadjusted cyanocobalamin concentrations at steady state in patients with vitamin B_{12} deficiency?

b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite its lower concentration-time profile pre- and post-administration.

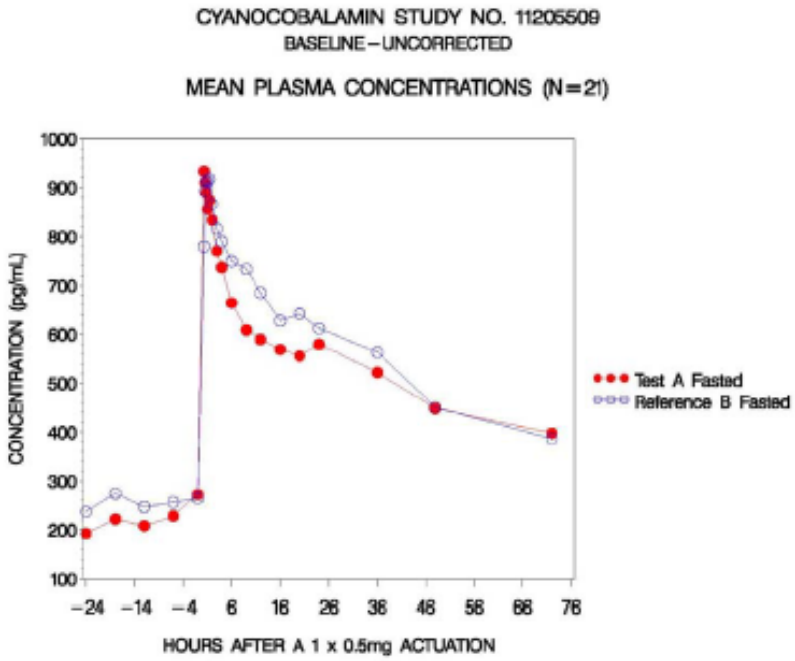
Par requests clarification if the Agency is requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 hr) geometric T/R ratio for unadjusted concentration data, as determined from the analysis of variance (Table 11.4.1.3 in the clinical study report),** is higher **at 1.0590**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.1 in the clinical study report).**

Table 11.4.1.3 Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Baseline-Uncorrected Cyanocobalamin-Primary Bioequivalence

Parameter	Test A	Reference B	Ratio	CI**	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	31164.66	29428.96	1.0590	0.9208 - 1.2179	26.6343
Cmax (pg/mL) (N=21)*	858.98	859.21	0.9997	0.8711 - 1.1473	26.2127

*N=Number of subjects with evaluable data for both the test and reference products.
**Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Figure 14.2.1 Mean Plasma Concentration versus Time Plot (Linear): Baseline-Uncorrected Cyanocobalamin (Primary Bioequivalence)



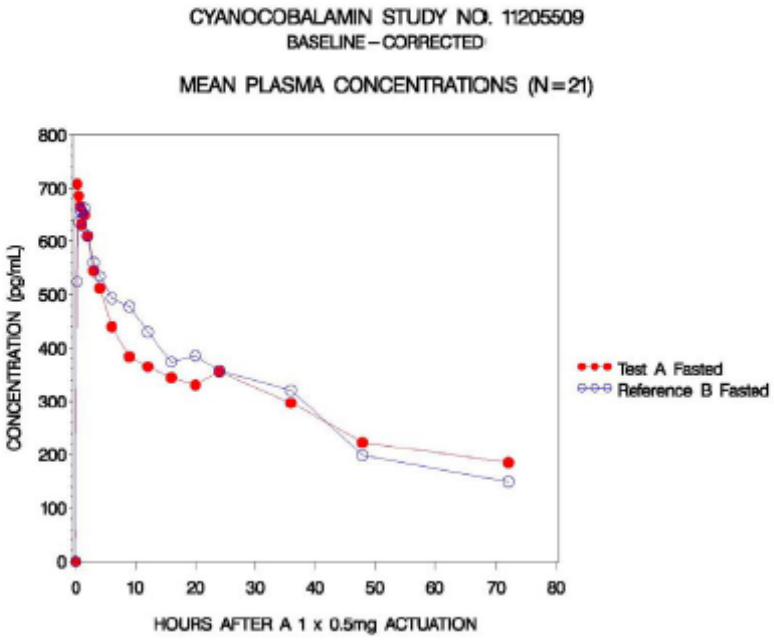
Or is the Agency requesting provision of a justification as to why the cyanocobalamin **AUC_{0-t} (t = 72 hr) geometric T/R ratio for baseline-corrected concentration data, as determined from the analysis of variance (Table 11.4.1.6 in the clinical study report),** is higher **at 1.1894**, despite its lower **mean** concentration-time profile pre- and post-administration **(Figure 14.2.3 in the clinical study report).**

Table 11.4.1.6 Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Baseline-Corrected Cyanocobalamin-Informational

Parameter	Test A	Reference B	Ratio	CI	Intra-Subject %CV
AUC0-t (pg·hr/mL) (N=21)*	17788.15	14955.73	1.1894	0.8092 - 1.7483	82.5776
Cmax (pg/mL) (N=21)*	674.57	648.84	1.0397	0.8784 - 1.2305	32.3513

*N=Number of subjects with evaluable data for both the test and reference products.

Figure 14.2.3 Mean Plasma Concentration versus Time Plot (Linear): Baseline-Corrected Cyanocobalamin (Informational)



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/s/

JENNIFER L JOHNSON
10/31/2013
Comments from ONDQA Biopharmaceutics review dated 10/25/13

From:	Johnson, Jennifer
To:	"Selby, Meredith"
Bcc:	Johnson, Jennifer
Subject:	NDA 21-642/S-020 T-con (8/14/2013) - *FDA follow-up responses and decision regarding BE study*
Date:	Friday, September 20, 2013 12:07:00 PM

Dear Meredith,

Thank you again for the teleconference discussion on August 14th and the follow-up written responses and clarification sent on August 26th. We have discussed your responses internally and have the following decision and comments to convey:

1. Upon further consideration, we believe that a difference of less than 20% in the mean baseline-corrected AUC for cyanocobalamin following nasal administration from both devices may not be of clinical relevance, provided that the trough concentrations at steady state are above the recommended minimum concentration of 200 pg/mL. Overall, FDA considers that an additional BE study is not necessary, provided you submit the following:
   a. Provide information/data (e.g., modeling and simulations, published literature, etc.) demonstrating that the cyanocobalamin values at steady state are above 200 pg/mL and that the Cmax value reached at steady state is not of safety concern.
   b. Provide a justification as to why the cyanocobalamin AUC_{0-72} for the new device is higher when compared to that for the current device, despite its lower concentration-time profile pre- and post-administration.
   c. A post-marketing commitment study to monitor the levels of cyanocobalamin at steady state following administration with the new device. This commitment is to be fulfilled within 6 months of the approval of this supplement.

2. We have the following advice/recommendations for the conduct of any future BE studies involving your cyanocobalamin nasal spray product:
   a. The imputation method (e.g., BLOQ values being imputed as LLOQ, ½LLOQ, zero, missing, etc.) influences the value of AUC; however, the outcome of the BE study corrected for baseline (namely failed BE) does not change for this particular drug product. This information, along with the fact that the intra-subject mean baseline values were similar between periods, suggest that failing of the BE study is likely due to a higher variability in drug delivery from the new proposed product. This is further supported by the fact that BE analysis applied to baseline values (FDA internal analysis) showed BE among periods only when LLOQ was set to missing. However, as mentioned before, BE failed for baseline-corrected plasma levels independent of the method of imputation.
   b. Given the nature of the plasma concentration-time profile following the nasal route of administration and the high variability in the observed plasma concentrations from 36 to 72 hours, AUC_{0-72} should be the PK metric used in the demonstration of bioequivalence for your proposed product.
   c. The use of adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio

may be considered if the difference between them is less than 20%.

d. Given that the method of baseline adjustment (imputation approach) did not change the outcome of the BE results for this proposed product and it highly depends on the number of BLOQ values in pre-dose and post-dose concentrations, we cannot agree with your proposal of using the imputation value of 100 pg/mL (½LLOQ). Baseline correction should follow the FDA recommendations.

e. The use of baseline-adjusted PK is highly recommended for bioequivalence evaluation of cyanocobalamin-containing nasal spray products, as it is for any other endogenously found drug substance.

f. We recommend the development of a more sensitive analytical method for the quantification of cyanocobalamin in plasma in order to decrease the bias due to the method of imputation being implemented and to increase on the accuracy of the results.

Let me know if you have any questions after reviewing the above.

Kind Regards,
Jennifer

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From: Selby, Meredith [mailto:Meredith.Selby@parpharm.com]
Sent: Monday, August 26, 2013 3:30 PM
To: Johnson, Jennifer
Subject: NDA 21-642/S-020 T-con (8/14/2013)

Hi Jennifer,

This is just a follow up to our August 14, 2013 T-con with Par and the FDA to discuss the Biopharmaceutics review. During the t-con, Par suggested we follow up with written responses to the questions raised and answered during the t-con. These are included in the attached minutes from the t-con. I am also including a revised document "Par's Discussion Points for study 11205509, Amendment 1" which was previously sent to you by email on 8/5/2013 including a few clarifications based on the t-con. The revised document contains a few minor clarifications as well as an additional paragraph. The revisions are highlighted within the document. Hopefully these will facilitate Dr. Sharp's decision regarding our current Bioequivalence study. We look forward to hearing back from you in the next 1-2 weeks on the discussions at FDA and your decision regarding our current BE study and/or the need for a new study. As previously mentioned, the SAS files are

available if requested. Thank you.

Best regards,
Meredith

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Nascobal (Cyanocobalamin, USP) Nasal Spray
NDA 21-642/S-020

Minutes from Nascobal Unit Dose T-con with FDA held Wednesday, August 14, 2013 at 10am EST

Attendees from FDA:

Jennifer Johnson, Regulatory Project Manager, DMEP
Deepika Arora Lakhani, Ph.D. – Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)
Sandra Suarez Sharp, Ph.D. – Acting Biopharmaceutics Team Leader, ONDQA
Ramesh Raghavachari, Ph.D. – Post-marketing CMC Team Leader, ONDQA

Attendees from Par:

Meredith Selby, Director Regulatory Affairs
Michelle Bonomi-Huvala, Senior VP Regulatory Affairs
Suketu Sanghvi, Ph.D., Vice President Research & Development
Chandra Vattikonda, M.Pharm., Ph.D., Executive Director, Biopharmaceutics, (b) (4)
Naomi Musaji, PharmD, Director, Medical Affairs

1. FDA requested clarification on the method of baseline correction. Par responded that for each period the baseline was estimated from the mean of the five pre-dose concentrations and this value was used to correct each post-dose concentration (i.e., single-point baseline adjustment).

2. FDA requested information on endogenous cyanocobalamin levels over a longer than 24-hr period. FDA commented that post-dose concentrations should be corrected for circadian rhythm by use of matched baseline correction (i.e., point-by-point baseline adjustment). Par responded that the baseline was stable over at least 24 hr before dosing as shown by the similarity of each of the five mean baseline concentrations, but the estimations of those mean baseline values and the associated within-period variability were influenced by the high number of BLOQ values as demonstrated by the different results obtained with the different imputation methods.

3. FDA discussed that the issues associated with the BLOQ values would disappear if the LLOQ was lowered. Par responded that the LLOQ could not be lowered because of the more stringent requirements for method validation compared to when the original assay with the lower LLOQ was conducted for the original application. Par emphasized that the even if the LLOQ is lowered the intra-subject variability for baseline-corrected Cmax and

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AUC will still be high (> 50% as per data in Table 4 of the response). Par commented that high intra-subject variability (> 50%) was also observed for the baseline-corrected Cmax and AUC data presented in the SBOA for the Nascobal® nasal gel versus nasal spray study.

4. FDA requested information on the percentage of AUC_{inf} extrapolated from AUC_{24} and AUC_{72}. Par responded that Kel and AUC_{inf} estimations are considered unreliable in > 50% of the data sets as per the criteria outlined in the response, which makes estimations of the corresponding extrapolated portions also unreliable.

5. FDA commented that the FDA is very data driven and that imputation of data other than 0 was generally not accepted. Par explained that 90 of the 220 pre-dose concentrations were BLOQ and that this greatly affected the variability in the baseline estimates when an imputation of zero was done.

6. FDA asked if an ANCOVA was used with mean baseline as a covariate in the model. Par responded that the ANCOVA was also performed, but that as the mean baseline with the zero imputation was highly variable, the confidence intervals were thus still wide.

7. FDA commented on Table 3 in the response (Intra-subject variability of cyanocobalamin baseline concentrations for various imputations for BLOQ in study 11205509). (b) (4) clarified that data in this table are for baseline concentrations.

FDA Comment:

1. **Your justification provided to explain the failure of bioequivalence (BE) for the upper bound of the 90% CI for $AUC_{(0-t)}$ for the baseline-corrected cyanocobalamin data is not acceptable. Based on the review of the baseline cyanocobalamin data provided for the 24 hours prior to the administration of the dose, the levels of endogenous cyanocobalamin do not have very high variability. To support and justify the failure of BE for the corrected data, we recommend that you provided data to support the inherent variability of endogenous cyanobalamin: e.g., basal cyanocobalamin levels for a minimum period of 72 hours.**

Par Pharmaceutical (Par's) Points of Discussion:

In Par's previous response dated June 28, 2013 we explained that the failure of BE for the upper bound of the 90% CI for AUC_{0-t} for the baseline-corrected cyanocobalamin data is a direct result of the high intra-subject variability for this parameter. We proposed that the high intra-subject variability is influenced by five factors:

1. The high baseline contribution of endogenous to total post-dose cyanocobalamin concentrations,
2. The lack of any measureable baseline concentrations in only one of the two periods for some subjects (# 2, 10 and 14),
3. The large number of below the LLOQ (BLOQ) values reported during the baseline period: 10 subjects (# 1, 2, 3, 7, 10, 14, 17, 20, 22 and 23) had four or more BLOQ values, out of a possible five pre-dose samples (-24, -18, -12, -6 and -1 hour), in at least one of the two periods,
4. The mixture of measureable pre-dose concentrations and at least one pre-dose concentration BLOQ for the five pre-dose samples in several (15 of 44) periods, and
5. The similarity in magnitude of the assay lower limit of quantitation (LLOQ = 200 pg/mL) to the baseline concentrations.

We postulated that the latter three factors largely contribute to inaccurate estimations of the mean of the five pre-dose concentrations that is used to correct the post-dose concentrations, and correspondingly likely lead to inaccurate adjustment in the baseline-corrected AUC_{0-t}.

We have conducted additional analyses of the data from study 11205509 to demonstrate that 1) the estimations of the mean baseline concentration are indeed variable within each period and between the subjects in the two periods, and 2) the adjusted BE results are highly dependent on the method of baseline correction. Our conclusion is that baseline-corrected AUC_{0-72} data are unreliable and the failure of the study is a direct consequence of the unreliability of the baseline correction procedure and is not a result of product (device) differences.

Comparison of cyanocobalamin baseline concentrations within and between periods in study 11205509

Raw data:
Tables 1 and 2 below show the mean cyanocobalamin baseline concentrations in periods 1 and 2 and their associated within-period and between-subject variability at each of the five pre-dose sampling times in the two periods. Three methods of imputation for the BLOQ value were evaluated because of the high number of pre-dose BLOQ values (90 of a total of 220 in the two periods).

1. Replace BLOQ with 0 (current FDA-recommended procedure)
2. Replace BLOQ with 100 (one-half the LLOQ value)
3. Replace BLOQ with 200 (LLOQ value)

Table 1. Mean cyanocobalamin baseline concentrations (pg/mL) in period 1 of study 11205509 and their associated within-period and between-subject variability (n = 22 subjects).

Period 1		**Time (hours) (n = 22 per time point)**					**Overall Mean (n = 5)**	**Pooled Intra %CV**
	BLOQ Imputation	**-24**	**-18**	**-12**	**-6**	**0**		
Mean	0	194.39	247.20	231.44	226.59	269.05	233.73	31.05
	100	244.39	288.11	272.35	272.05	296.32	274.64	19.95
	200	294.39	329.01	313.26	317.50	323.60	315.55	13.56
Inter %CV	0	113.65	96.58	99.92	108.27	87.92	101.27	
	100	72.12	67.97	69.83	74.62	69.70	70.85	
	200	46.27	47.82	49.38	52.15	56.58	50.44	

Table 2. Mean cyanocobalamin baseline concentrations (pg/mL) in period 2 of study 11205509 and their associated within-period and between-subject variability (n = 22 subjects).

Period 2		**Time (hours) (n = 22 per time point)**					**Overall Mean (n = 5)**	**Pooled Intra %CV**
	BLOQ Imputation	**-24**	**-18**	**-12**	**-6**	**0**		
Mean	0	215.49	225.84	202.73	235.80	242.54	224.48	37.37
	100	260.94	262.20	252.73	272.17	278.90	265.39	21.15
	200	306.39	298.56	302.73	308.53	315.27	306.30	11.60
Inter %CV	0	104.08	93.59	113.04	88.83	90.57	98.02	
	100	68.96	65.94	72.85	61.85	64.34	66.78	
	200	45.75	47.31	47.31	43.05	45.96	45.88	

The mean values for each of the five pre-dose concentrations within each period are similar in magnitude, regardless of the method of BLOQ imputation, indicating the baseline is stable with minimal circadian fluctuation, at least over the 24-hour pre-dose period, and that the subjects were well stabilized on the low vitamin B_{12} diet. The shape of the mean concentration-time profiles over the 24-hour pre-dose sampling period is similar between periods 1 and 2 (see **Figures 1 and 2**).

Figure 1. Mean cyanocobalamin baseline concentrations in period 1 of study 11205509.

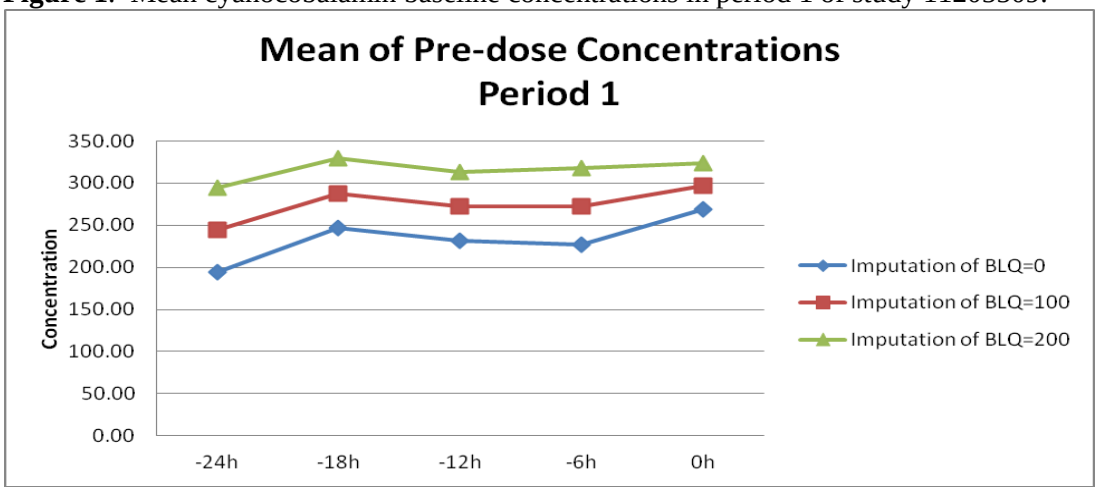
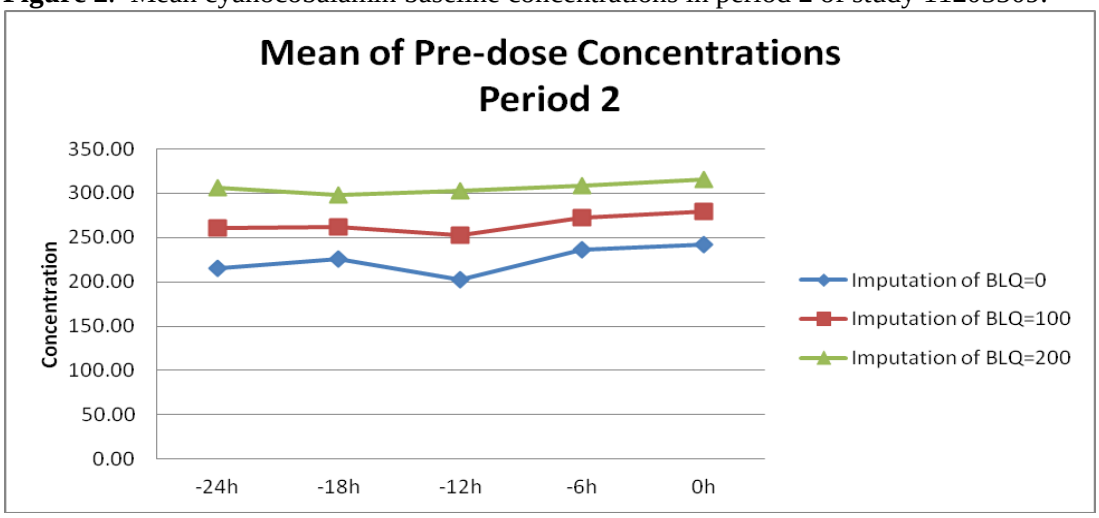


Figure 2. Mean cyanocobalamin baseline concentrations in period 2 of study 11205509.



However, the overall mean of the pre-dose concentrations, the within-period variability, and the between-subject variability at each of the five pre-dose sampling times are influenced by the imputation method. For example, the overall mean pre-dose concentration is lowest and the variabilities are highest when BLOQ values are replaced with 0, with inter-subject %CVs near 100% in each period and within-period %CVs of 31% for period 1 and 37% for period 2. Whereas the overall mean pre-dose concentration is highest and the variabilities are lowest when the BLOQ values are replaced with the LLOQ value of 200 pg/mL.

Ln-transformed data:
The pre-dose concentrations in periods 1 and 2 were also analyzed following ln-transformation of the data by a mixed model incorporating the fixed effects of period and time and random effect of subject. The BLOQ values could not be replaced with 0 so various imputations from the LLOQ value of 200 to one-eighth of the LLOQ (25 pg/mL) were assessed for the 21 subjects (subject # 20's data excluded). There was no period-by-time interaction for each of the different imputations. The results showed that the intra-subject variability, which is a measure of the consistency of the difference between the baseline

concentrations at the different sampling times within a subject pooled over all subjects, increases from 16% to 94% as the imputation approaches 0, further supporting that an imputation of 0 for BLOQ, as was done in the originally submitted data, magnifies variability (see **Table 3** below).

Table 3. Intra-subject variability of cyanocobalamin baseline concentrations for various imputations for BLOQ in study 11205509.

Imputation for BLOQ	Pooled Intra-subject %CV for pre-dose concentrations
LLOQ = 200	15.53
½LLOQ = 100	35.14
¼LLOQ = 50	61.31
⅛LLOQ = 25	93.88

Conclusions on baseline data in study 11205509

1. The different methods of imputation for BLOQ values (0, 100 and 200) give different overall mean pre-dose concentrations and within-period and between subject %CV values.
2. The high number of BLOQ values for the pre-dose concentrations leads to high within-period variability for the estimation of each subject's mean pre-dose concentration in the two periods when BLOQ is replaced with 0.
3. This high within-period variability for BLOQ imputations of 0 potentially led to inaccurate estimation of each subject's mean pre-dose concentration that was used to correct the post-dose concentrations in each period.

Baseline adjustment of post-dose concentrations in study 11205509

In the originally submitted data, the post-dose concentrations were adjusted for baseline by subtracting the mean of the five pre-dose concentrations (with imputation of 0 for BLOQ values) from the individual post-dose concentrations. The pre-dose concentration at time 0 was *a priori* set to the mean pre-dose value. Negative baseline-corrected values were set to 0 as recommended in FDA individual bioequivalence guidances. This method is hereinafter referred to as the FDA method. We performed additional analyses of the FDA method with imputation of 100 (½LLOQ) and 200 (LLOQ) for the pre-dose and post-dose BLOQ values. We also re-analyzed the AUC data using a different method of baseline adjustment by keeping the negative baseline-corrected values in the analysis. In this method, hereinafter referred to as the Par method, the pre-dose and post-dose BLOQ values were also imputed as 0, 100 or 200, as in the FDA method. We believe this is a more mathematically correct way to baseline adjust the data. Because concentrations approached the LLOQ after 24 hours in some subjects, AUC_{0-24}, in addition to AUC_{0-72} and C_{max}, was analyzed with unadjusted and baseline-adjusted data for both methods. Data from subject # 20 were excluded in all analyses because there was only one post-dose concentration in period 1. The results for the FDA and Par baseline-correction methods using the three different imputation methods are presented in **Table 4** below.

Table 4. Bioequivalence results for study 11205509 using the FDA and Par baseline correction methods and different imputation methods for BLOQ values.

Imputation	A/B ratio (%)	90% lower CL	90% upper CL	Pooled intra-subject %CV
Ln(Cmax)				
Unadjusted	99.73	87.11	114.73	26.21
0 (FDA or Par)	103.97	87.84	123.05	32.35
100 (FDA or Par)	102.71	86.17	122.42	33.77
200 (FDA or Par)	99.19	80.75	121.84	39.98
Ln(AUC_{0-72})				
Unadjusted	105.90	92.08	121.79	26.63
0 (FDA)	118.94	80.91	174.83	82.58
100 (FDA)	119.42	82.35	173.17	78.89
200 (FDA)	119.14	81.39	174.42	81.46
0 (Par)	87.19	64.61	117.66	57.92
100 (Par)	90.69	69.44	118.43	50.53
200 (Par)	95.83	70.11	130.98	60.22
Ln(AUC_{0-24})				
Unadjusted	96.29	85.38	108.61	22.82
0 (FDA)	103.75	78.01	137.99	57.42
100 (FDA)	104.69	79.43	138.00	55.35
200 (FDA)	102.82	76.67	137.89	59.35
0 (Par)	103.79	77.04	139.83	60.42
100 (Par)	110.29	77.58	156.79	73.68
200 (Par)	92.50	70.17	121.93	53.94

Regardless of the baseline-correction and imputation methods the pooled intra-subject %CV values remain high at > 50% for the AUC parameters. However, the baseline-correction method has a large influence on the ratios and %CVs for AUC_{0-72}, with adjusted ratios closer to 100% and smaller %CVs for the Par method. The adjusted AUC_{0-24} ratios are closer to 100% than are the adjusted AUC_{0-72} ratios, particularly for the FDA method. There are larger differences in adjusted AUC_{0-24} ratios for the Par method depending on the imputation method. Though most concentration-time profiles show positive baseline-corrected values, all these differences in adjusted AUC ratios are a consequence of the comparatively high number of zero and negative baseline-corrected concentrations in the post-absorption phase (see **Table 5**), suggesting that baseline adjustment of AUC data is not recommended for study 11205509.

Table 5. Number of post-dose baseline-corrected values that result in 0 or negative values for various imputations for BLOQ in study 11205509.

Imputation for BLOQ	Number of 0 concentrations	Number of negative concentrations
LLOQ = 200	21	15
½LLOQ = 100	21	13
0	21	11

A listing of each subject's concentrations from -24 hours to 72 hours post-dose for unadjusted concentrations is in the 11205509_unadjusted.xpt SAS file. Excluding data from subject # 20 there are 25 post-dose BLOQ values from six subjects (# 2, 3 14, 17, 21 and 22). Most of the BLOQ values occur for subject # 17. Listings of the baseline-adjusted post-dose concentrations for the different imputation methods (0, 100, 200) are in the 11205509_0_adjusted.xpt, 11205509_100_adjusted.xpt, and 11205509_200_adjusted.xpt SAS files, respectively. The numbers of zero and negative concentrations that result from the baseline adjustment are shown in **Table 5** above (subject # 20 excluded). Most of the zero and negative concentrations are associated with subjects # 17 and 21, respectively. Zero concentration values result when both the mean pre-dose concentration and the post-dose concentration are BLOQ.

There is minimal decline in baseline-corrected concentration from 20 hours onwards, which suggests there is very slow release of vitamin B_{12} from tissues following administration and/or the estimated mean baseline concentration over the 24-hour period before dosing may not be a reflection of post-dose endogenous concentrations for accurate baseline correction of post-dose concentrations over the 72-hour sampling period. The latter is likely an inherent characteristic of vitamin B_{12} pharmacokinetics considering vitamin B_{12} undergoes entero-hepatic recycling.

To further examine the value of AUC_{0-24} as a bioequivalence parameter and the effect of imputation of BLOQ values, an analysis of the ratio of adjusted AUC_{0-t} to unadjusted AUC_{0-t} was performed. The adjusted AUC_{0-t} was estimated as the sum of the observed AUC_{0-24} and the predicted AUC_{24-t}. The predicted AUC_{24-t} was assumed to result only from endogenous cyanocobalamin and was calculated as mean baseline multiplied by the time interval from 24 to t hours. **Table 6** summarizes the results of the ratio of adjusted AUC_{0-t} to unadjusted AUC_{0-t} for various imputations for BLOQ.

Table 6. Ratio (%) of [AUC_{0-24} + (mean baseline *x* (t-24))]/ AUC_{0-t} using imputation of BLOQ values of 0, 100 and 200 in study 11205509.*

Treatment \ Imputation	BLOQ=0	BLOQ=100	BLOQ=200
A	66.13	76.43	86.73
B	72.57	84.68	96.78

*Note: t varied by subject according to observed time of last measurable concentration

Results show that when the BLOQ values are imputed with ½LLOQ, the ratio of adjusted AUC_{0-t} to unadjusted AUC_{0-t} is on average about 80%. This is consistent with cyanocobalamin concentrations returning to near baseline level after about 24 hours, thus supporting AUC_{0-24} as a suitable parameter for to evaluate total systemic exposure and bioequivalence of cyanocobalamin-containing nasal spray products.

Attempted estimations of terminal rate constant (λ_z), terminal half life ($t_{½,z}$), and $AUC_{0-\infty}$

In Par's previous response dated June 28, 2013, theoretical reasons were provided to justify not providing the requested baseline-corrected cyanocobalamin data for the $t_{½,z}$, λ_z and $AUC_{0-\infty}$ parameters. As part of the additional analyses of the data from study 11205509 we attempted to estimate the three parameters to further support those arguments. The data set with imputations of 0 for BLOQ values was used. At least three sampling times (not including Tmax) were included in the estimations of λ_z. The following criteria were used to determine if the estimate of λ_z was considered reliable:

1. The adjusted R^2 value from the linear regression is > 0.8, and

2. The associated $t_{½,z}$ is shorter than the time span over which λ_z is estimated, as proposed by Purvis (Method 1),[1] or
3. The associated $t_{½,z}$ is shorter than half of the total sampling interval or shorter than half of the time of last measureable concentration (t_{last}) if t_{last} is less than the time of last sample collection, as proposed by Colucci et al (Method 2).[2]

If λ_z was considered reliable then $t_{½,z}$ and $AUC_{0-\infty}$ were estimated. $AUC_{0-\infty}$ was considered reliable if the extrapolated portion from AUC_{0-t} was < 20%.

Using Method 1, 18 of 42 (43%) data sets have reliable λ_z estimates and using Method 2, 13 of 42 (31%) data sets have reliable λ_z estimates. A listing of the $AUC_{0-\infty}$ values calculated from baseline-adjusted post-dose concentrations using 0 for imputation of the BLOQ values are in the 11205509_AUCinf.xpt SAS file. The reliable estimates all have associated $t_{½,z}$ values that are < 30 hours. Of the 30 data sets with adjusted R^2 values of > 0.8, 25 have associated $t_{½,z}$ values of > 24 hours (i.e., long elimination half life, as defined in FDA's Draft Guidance on Amiodarone Hydrochloride, December 2010); most of these half lives are longer than the time span over which λ_z is estimated (Method 1) or longer than half of t_{last} (Method 2). This further supports that cyanobalamin has a long terminal half life such that truncation of AUC to 72 or 24 hours is warranted. Ten (10) of 42 data sets have reliable $AUC_{0-\infty}$ estimates and only two subjects (# 15 and 18) have reliable $AUC_{0-\infty}$ values in both periods.

These results strongly support that estimations of λ_z and $AUC_{0-\infty}$ parameters from baseline-adjusted data are not appropriate for cyanocobalamin in study 11205509, as originally proposed in Par's previous response.

Conclusions on baseline-correction in study 11205509

1. The method of baseline adjustment influences the value of AUC_{0-72} as a result of the high number of BLOQ values in pre-dose and post-dose concentrations, the high number of zero and negative baseline-corrected post-dose concentrations, and the high contribution of the baseline concentrations to AUC_{0-72}.
2. Adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio is likely more representative of the true AUC ratio because of the "noise" in the post-dose concentrations from 36 to 72 hours.
3. Estimations of λ_z and $AUC_{0-\infty}$ from baseline-corrected data are unreliable in more than 55% of the 42 data sets. Even for the reliable estimates of λ_z the estimated half lives are not the clinically relevant or physiologically effective disposition half life, as they would be too short (< 30 hours) to explain the expected drug accumulation over 4 weeks to steady state following once-weekly intra-nasal dosing of cyanocobalamin-containing nasal spray products.[3]

<u>Overall Points of Clarification:</u>

1. In study 11205509 the endogenous cyanocobalamin baseline was stable over the 24-hour pre-dose period in the two periods but high within-period variability for BLOQ imputations of 0 was demonstrated, which potentially could have led to inaccurate estimation of each subject's mean pre-dose concentration that was used to correct the post-dose concentrations in each period.

2. Baseline-corrected AUC_{0-72} is not a reliable parameter to demonstrate bioequivalence in study 11205509 because of the "noise" in the post-dose concentrations from 36 to 72 hours.
3. The failure of study 11205509 to demonstrate bioequivalence for AUC_{0-72} is a direct consequence of the unreliability of the baseline correction procedure and is not a result of product (device) differences.
4. We propose that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to evaluate bioequivalence of cyanocobalamin-containing nasal spray products. Evaluation of $AUC_{0-\infty}$ is not appropriate.
5. For an LLOQ value of 200 pg/mL in future studies, an imputation value of 100 pg/mL (½LLOQ) has scientific rationale for minimizing the bias and within-period variability in the estimation of the mean pre-dose concentration for use in baseline adjustment of post-dose concentrations.
6. If baseline-adjusted AUC is a requirement for bioequivalence evaluation of cyanocobalamin-containing nasal spray products then Par proposes that adjusted AUC_{0-24} rather than adjusted AUC_{0-72} test-to-reference ratio may be a better parameter to demonstrate bioequivalence of this product.
7. If confidence limits around the test-to-reference ratio are required to be within 80-125% then Par proposes to repeat the study with a reference-replicated design to accommodate the high within-subject variability in AUC_{0-24} and AUC_{0-72} (> 50%) induced by the baseline adjustment. BLOQ values will be imputed as ½LLOQ and both the FDA and Par baseline correction procedures will be evaluated if the LLOQ of the assay remains at 200 pg/mL. Every effort will be made to lower the assay LLOQ from 200 pg/mL. Par believes that sampling over a 72-hour pre-dose period is not necessary to demonstrate the stability of basal cyanocobalamin levels as recommended by FDA, considering the stability of the baseline over 24 hours.

References

1. Purves RD. Bias and variance of extrapolated tails for area-under-the-curve (AUC) and area-under-the-moment-curve (AUMC). *J Pharmacokinet Biopharm.* 1992;20(5):501-510.
2. Colucci P, Turgeon J, Ducharme MP. How critical is the duration of the sampling scheme for the determination of half-life, characterization of exposure and assessment of bioequivalence. *J Pharm Pharmaceut Sci.* 2011;14(2):217-217.
3. Product Label for Nascobal® (Cyanocobalamin, USP) Nasal Spray, 500 mcg/spray. Par Pharmaceutical Companies, Inc. (Manufactured for QOL Medical, LLC) February 2006.

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/s/

JENNIFER L JOHNSON

09/20/2013

Comments and decision from ONDQA Biopharmaceutics review dated 9/17/13 by Sandra Suarez and Angelica Dorantes sent to sponsor following teleconference with sponsor on 8/14/13 to discuss and clarify what is needed for Complete Response resubmission for CMC supplement S-020 (CR letter issued on 7/12/13); sponsor tcon minutes and post-tcon written responses from 8/26/13 email included

From:	Johnson, Jennifer
To:	Selby, Meredith (Meredith.Selby@parpharm.com)
Bcc:	Johnson, Jennifer
Subject:	NDA 21642/S-020 (Nascobal Nasal Spray): Labeling Comments + Request for Samples
Date:	Tuesday, August 06, 2013 6:58:00 PM

Dear Meredith,

We have reviewed the labeling submitted to NDA 21642/S-020, Nascobal (cyanocobalamin) Nasal Spray, and have the following comments and recommendations:

A. Container Label

1. (b) (4)

2. Revise and relocate the strength of the product, ("500 mcg/spray" or "500 mcg per spray"), to appear below the proprietary and established names.
3. If space permits, incorporate the net quantity statement to read "1 spray" or "1 spray per device".
4. Ensure that the first 10 characters of the linear bar code represent the National Drug Code as per 21 CFR 207.35.

B. Blister Labeling (Trade and Professional Sample)

1. Each blister should contain the expiration date and lot number per 21 CFR 201.17.
2. Relocate the strength statement to appear on a separate line of text directly below the established name.
3. Relocate the route of administration statement "For nasal use only" to appear directly below the strength statement.
4. The spray bottle that this single dose device is replacing required priming before each dose, thus the patient may attempt to "prime" this new device before use leading to drug loss and under dosing errors. As a result, we recommend the statement (b) (4) be revised to read "Do not prime before use" since the previous labeling referred to "priming" the device (b) (4)

5. Consider increasing the prominence of the statement "1 spray per device" and "Do not prime before use."

C. Carton Labeling (Trade and Professional Sample)

1. See recommendation A.2.
2. We recommend that the patient instructions for use be retained on the side panel. Although the package insert is included in the carton, it may be separated from the packaging and having the instructions for use on the carton would provide an alternate place the patient can refer to how to use the device.
3. Revise the established name (i.e., active ingredient and dosage form) to appear with equal prominence similar to the proposed presentation on the container label.

The revised labeling should be included in your planned Complete Response submission.

Also, we are requesting samples of your proposed product presentation.

Please send these to me at the following address:
Jennifer Johnson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3114
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
08/06/2013
Labeling comments from DMEPA review dated July 12, 2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Mail: OSE (Teena Thomas)

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Priyanka Kumar, ONDQA, Division of Metabolic and Endocrine, Post Marketing, 240-402-3722

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/6/2013		21642	S-020	3/13/2013

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nascobal ® (cyanocobalamin, usp) Spray			6/30/2013

NAME OF FIRM: Par Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☒ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This PAS provides for a new unit dose device. Upon approval this unit dose device will replace the current packaging configuration of 1.3mL, once current inventory is depleted. The final printed labeling for the unit dose device, including the device container labeling, blister labeling (for trade and sample) is included in Module 1.14.2. The proposed package insert is also included in 1.14.2. The insert has been revised to modify the Dosage and Administration section, how supplied section, and pharmacist assembly instruction. The PDUFA Goal date is 7/12/2013.

SIGNATURE OF REQUESTOR
Priyanka Kumar

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

PRIYANKA KUMAR
06/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Mail: OSE (Teena Thomas)

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Priyanka Kumar, ONDQA, Division of Metabolic and Endocrine, Post Marketing, 240-402-3722

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/6/2013		21642	S-020	3/13/2013

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nascobal ® (cyanocobalamin, usp) Spray			6/30/2013

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

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- ☐ END-OF-PHASE 2 MEETING
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- ☒ CHEMISTRY REVIEW
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- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

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SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Priyanka Kumar	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

PRIYANKA KUMAR
06/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21642/S-020

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Par Pharmaceuticals, Inc.
Attention: Meredith Selby
Director, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Selby:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21642

SUPPLEMENT NUMBER: S-020

PRODUCT NAME: Nascobal® (cyanocobalamin) Spray

DATE OF SUBMISSION: March 11, 2013

DATE OF RECEIPT: March 12, 2013

This supplemental application proposes the following change: To supply Nascobal® Nasal Spray in a unit-dose device.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 11, 2013 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 12, 2013.

If you have questions, call me at (240) 402-3722

Sincerely,

{See appended electronic signature page}

Priyanka Kumar, Pharm. D
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRIYANKA KUMAR
05/13/2013