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APPLICATION NUMBER:

21-642

MEDICAL REVIEW(S)

10/19/04

Medical Team Leader Memo

NDA #:	21-642
Sponsor:	Nastech Pharmaceutical Company, Inc.
Drug	Nascobal® (cyanocobalamin, USP) Spray for Intranasal Administration
Date of submission:	December 26, 2003 (received 12/31/03)
Reviewer:	Mary H. Parks, MD

Summary of Application

Nastech Pharmaceutical Company has submitted an NDA for the approval of an aqueous solution of cyanocobalamin to be administered as a metered-dose nasal spray in the maintenance treatment of patients with Vitamin B12 deficiency. The clinical study supporting this application includes a BE study comparing the nasal spray formulation to the currently marketed, intranasally-administered gel formulation.

This study was a single-site, open-label, 3-way crossover pK study conducted in healthy male and female subjects. Treatment groups included vitamin B12 administered via intranasal spray at 500 ug, IN gel administered at 500 ug, and IM injection at 100 ug. The study was conducted under fasting conditions.

In the study report, bioequivalence was reported to be established between the two intranasal formulations but, as expected, was less bioavailable than the IM formulation. Dr. Jaya Vaidyanathan of the Office of Clinical Pharmacology and Biopharmaceutics noted that baseline corrections for B12 levels were not done in the sponsor's analysis. After correcting for baseline values, Dr. Vaidyanathan noted that the intranasal spray was 10% less bioavailable than the IN gel.

The applicant stated that the nasal spray was reformulated without methylcellulose and [redacted] It is unclear whether this [redacted] between the two formulations fully explains the findings from the bioequivalence study.

While this product cannot be considered bioequivalent to the reference listed product, the clinical use of this product or any cyanocobalamin formulation requires the monitoring of patients to determine if adequate repletion of B12 has been achieved. Patients not achieving adequate B12 levels require increased dosing with subsequent blood monitoring. It should also be noted that the indication for Nascobal is for patients previously treated with IM cyanocobalamin and should, therefore, have adequate hepatic stores of B12 at the time of switch to an intranasal formulation.

Labeling for this product, however, will require a discussion of the difference in pharmacokinetics of the two products and that patients treated with the nasal spray should have vitamin B12 levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.

Other review issues identified in this NDA include a manufacturing facility that is not yet ready for inspection. Until this facility is inspected and found to be acceptable, this application will be approvable.

Labeling is deferred until resubmission to this NDA. The action letter should inform the applicant that a 10% difference in bioequivalence was noted between the two intranasal formulations. The applicant should submit revised labeling to describe these pK results and how these results will affect clinical monitoring and dose adjustments.

Financial disclosure information was submitted with this application and found to be acceptable.

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/s/

Mary Parks
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MEDICAL OFFICER