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APPLICATION NUMBER:

22-102

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

6/21/07

OFFICE OF CLINICAL PHARMACOLOGY

NDA:	22-102
Submission Date(s):	9/26/2006; 2/16/2007
Brand Name:	[redacted] Nasal Spray
Generic Name:	Cyanocobalamin
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Sally Choe, Ph.D. (Acting)
OCP Division:	DCP 2
ORM Division:	DMEP
Sponsor:	Fleming & Company, Pharmaceuticals
Relevant IND:	58346
Submission Type:	505(b)(2)
Formulation (Strength):	A metered dose spray in 30mL plastic bottles containing 18mL
Indication:	[redacted]
Dosage and Administration:	One spray in each nostril daily (25mcg per nostril, total daily dose 50 mcg)

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the analytical validation of NDA22-102 for ——— and finds it acceptable. b(4)

1.2 Phase IV Commitments

N/A

1.3 Summary of Clinical Pharmacology Findings

The sponsor submitted the NDA 22-102 for ——— Nasal Spray (cyanocobalamin) as the 505(b)(2) referencing Nascobal® Nasal Spray (NDA 21-642). The approved dosing regimen of the Nascobal® is one spray (500 mcg) in one nostril once weekly and the proposed dosing regimen of the ——— is one spray in each nostril daily (daily dose 50 mcg). b(4)

The sponsor conducted one study (PR99-063) for the safety and efficacy of ———. The primary objective of study was to evaluate whether daily intranasal (IN) administration of ——— Nasal Spray was sufficient to maintain serum vitamin B12 levels over an 8-week period in patients who previously had intramuscular (IM) injections (n=24). Blood samples were collected to evaluate vitamin B12 concentrations based on the patient visit schedule (Table 1) and the serum vitamin B12 concentration-time profile was shown in Figure 1. It was concluded that ——— maintained vitamin B12 levels without significant safety issues. Formulation used in the pivotal study (PR99-063) was the same as the commercial formulation. b(4) b(4)

Table 1 Summary of Visit Schedule

Prestudy	Screening	Treatment Period		
←——2-4 weeks ——→	←—— 2-4 weeks ——→	←———————— 8 weeks ————————→		
B_{12} IM injection	Study enrollment	Start OCEANS-12		Final visit
	Visit 1	Visit 2*	Visits 3-5	Visit 6
	Week -2 to -4	Day 0	Weeks 2-6	Week 8

* Note: Visit 2 blood samples for B_{12} levels were drawn prior to study drug administration.

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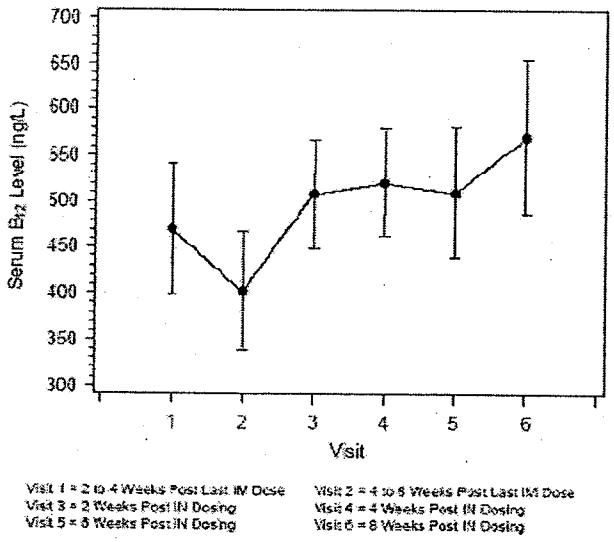

Figure 1 **Mean (SD) serum vitamin B12 concentrations over treatment period in subjects stabilized on intramuscular vitamin B12.**

The clinical review covered the evaluation of vitamin B12 exposure as one of efficacy endpoints and there were no additional issues to be reviewed from clinical pharmacology perspective except analytical validation.

The sponsor did not submit the assay methods and validation with the original NDA. As a response to the Agency's filing letter, the sponsor submitted a brief summary of assay methods and validation for vitamin B12, folate, and markers of B12 dependent metabolism (i.e., homocystein, and methylmalonic acid) on February 16, 2007. Clinical laboratory analyses were conducted by . ——— b(4)
——— Vitamin B12 and folate were analyzed by a ———
method, homocystein was analyzed by a ———
and methylmalonic acid was analyzed by ——— method. The coefficient of variation for b(4)
accuracy and precision was less than — for the above mentioned compounds except homocystein near the QL —— (Table 2).

Overall, the validation of assay methods was acceptable.

Table 2 Summary of the validation report

Vitamin B12 and folate

Validation Characteristic	Summary of Results
Specificity	• No interferences were observed from plasma with or without EDTA. Samples containing ascorbic acid, heparin, fluoride or hemolyzed red blood cells may exhibit interference and should not be used or else noted appropriately with this test.
Accuracy	• Acceptable recovery ($r > 0.999$) was found for various spikes within the measurement range.
Precision	• Multiple replicate measurements in the B_{12} ranges of 225-300 and 400-700 pg/mL gave CV values of 8% and 6%, respectively; multiple replicate measurements in the folate ranges of 2.0-3.0 and 2.5-8.0 pg/mL gave CV values of 9% and 7%, respectively.
Linearity	• For B_{12}, acceptable linearity ($r = 0.998$) was observed from 100-2000 pg/mL • Parallelism was demonstrated ($r > 0.999$) using serial dilutions within the measurement range.
Sensitivity	• For B_{12}, a QL of 1.2 pg/mL was found.
Robustness	• Serum is stable for at least 2 days at ambient temperature, 5 days at 5°C, and 14 days at -20°C.
Range	• Based on a combination of the accuracy, precision and linearity results, the method is validated from at least 100-2000 pg/mL B_{12}.

Homocystein

Validation Characteristic	Summary of Results
Specificity	• No interferences were observed from bilirubin, triglycerides, hemolyzed red blood cells, EDTA plasma and heparinized plasma samples.
Accuracy	• An average recovery of 101% was found for 13 samples spiked with four different levels of homocysteine within the measurement range.
Precision	• Multiple replicate measurements near the 50 µmol/L level gave CV = 4%; 45 replicate measurements near the QL gave CV = 16%.
Linearity	• Acceptable linearity was observed from the QL to at least 50 µmol/L • Parallelism was demonstrated using serial dilutions within the measurement range.
Sensitivity	• QL ≤ 1.8 µmol/L
Robustness	• Serum is stable for at least 2 days at ambient temperature, 4°C, -20°C and -70°C. • The results obtained by this method are similar to those obtained by GC/MS (from a plot of results of one method vs the other, slope = 0.98, r = 0.98; and from paired t-test, p = 0.71).
Range	• Based on a combination of the accuracy, precision and linearity results, the method is validated from the QL to at least 50 µmol/L.

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Methylmalonic acid

Validation Characteristic	Results		
Accuracy	[MMA] (nanomol/L)	Samples	Recovery (%)
	≤ 200 600 ≥ 1200	8 4 3	90-106 99-104 101-104
Precision (intralaboratory)	[MMA] (nanomol/L)	Samples	% CV
	250 650 2000	10 10 12	3.0 5.7 2.5
Precision (interlaboratory)	243 764 2090	22 22 22	4.9 4.7 4.0
Linearity	• Acceptable linearity is observed from the QL to at least 2000 nanomol/L • Parallelism was demonstrated using serial dilutions within the measurement range.		
Sensitivity	• DL ≤ 50 nanomol/L • QL ≤ 100 nanomol/L		
Robustness	• Serum is stable under the following conditions: – At least 4 days at 18-25°C – At least 1 week at 4°C – At least 10 months at -20°C – At least 2 freeze/thaw cycles • A comparison of 148 samples run in a manual and automated manner gave an r ≈ 0.9999.		
Range	• Based on a combination of the accuracy, precision and linearity results, the method is validated from 100 to at least 2000 nanomol/L. In actual practice, results from 100 to 4000 nanomol/L may be reported.		

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2 Attachment

2.1 Synopsis

SYNOPSIS

Name of Sponsor/Company: Fleming & Company, Pharmaceuticals	
Name of Finished Product: ——Cyanocobalamin, USP) Spray for Intranasal Administration	
Name of Active Ingredient: Cyanocobalamin, USP	
Title of Study: Nasal Delivery of Vitamin B_{12}	
Protocol No: PR99-063	
Investigators: Mark S. Dykewicz, MD, FACP	
Study center: Saint Louis University, St. Louis, MO	
Publication (reference): Not applicable	
Studied period: 10 March 2000 to 27 June 2002	**Phase of development:** pivotal
Objectives: To determine if daily intranasal (IN) administration of cyanocobalamin (vitamin B_{12}) in physiological saline is sufficient to maintain normal serum vitamin B_{12} levels over an 8-week period in patients who previously have required intramuscular (IM) vitamin B_{12} injections to maintain normal serum B_{12} levels.	
Methodology: This was an open-label study, where all patients received daily intranasal administration of vitamin B_{12} for an 8-week treatment period.	
Number of patients: 20-35 patients planned, 30 enrolled, 25 analyzed	
Diagnosis and main criteria for inclusion: This study included patients with documented vitamin B_{12} deficiency who had been receiving maintenance IM injections of vitamin B_{12} and who had a normal serum level at study entry.	
Test product, dose and mode of administration, batch number: Patients self-administered 1 puff of vitamin B_{12} nasal spray daily in each nostril (daily dose 50 µg cyanocobalamin). Batch numbers: 9036 and 0060116	
Duration of treatment: 8 weeks **Duration of study:** 10-12 weeks	
Reference therapy, dose and mode of administration, batch number: Not applicable	

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Name of Sponsor/Company: Fleming & Company, Pharmaceuticals
Name of Finished Product: [redacted] (Cyanocobalamin, USP) Spray for Intranasal Administration
Name of Active Ingredient: Cyanocobalamin, USP
Criteria for evaluation: Efficacy: Efficacy was measured by levels of vitamin B_{12}. Homocysteine and methylmalonic acid levels were also assessed. Poststudy patient assessment of the product was evaluated by a product assessment form. Safety: Safety was measured by adverse events (AEs), clinical laboratory tests, physical examination, and vital signs.
Statistical methods: Efficacy: The primary efficacy analysis was based on the evaluation of the ratio of the posttreatment B_{12} levels Visits 3-6 relative to Visit 1 values. A repeated measures model was fit that modeled the ratio as a function of visit with the patient being treated as a random effect. The 90% two-sided confidence interval (CI) was calculated for the average ratio observed from Visits 3 through 6. An a priori success criteria was established that deemed [redacted] equivalent if the lower bound of the confidence of the interval was greater than 0.8. Standard descriptive statistics were provided for the observed B_{12} values, the ratio of post-Visit 1 B_{12} values to the Visit 1 B_{12} value, the change from baseline in observed values, the change from baseline in log-transformed B_{12} values, and the ratio of the B_{12} value at each visit divided by the therapeutic threshold of 200 ng/L. The statistics were calculated by visit. Homocysteine levels, methylmalonic acid levels, and poststudy product assessment form results were summarized descriptively. Safety: AEs were tabulated by system organ class. Descriptive statistics were performed for clinical laboratory tests and vital signs. Physical examination results were listed for each patient.

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Name of Sponsor/Company:
Fleming & Company, Pharmaceuticals

Name of Finished Product:
[redacted] (Cyanocobalamin, USP) Spray for Intranasal Administration b(4)

Name of Active Ingredient:
Cyanocobalamin, USP

Summary—Conclusions

Efficacy Results:

The efficacy analyses indicated that the [redacted] nasal spray was effective at maintaining vitamin B_{12} levels in patients who had previously been stabilized on IM B_{12} injections. For all posttreatment visits (Visits 3-6) and the average of all treatment visits, the observed ratio of values relative to baseline was greater than 1. For the primary efficacy analysis, the mean ratio of Visits 3-6 to Visit 1 was 1.15 (90% CI 1.06, 1.24) and statistically significant (p=0.0096), while other comparisons were marginally statistically significant. With the exception of Visit 3, the lower bound of the two-sided 90% CI was greater than 1. b(4)

Review of individual patient results demonstrated variability between patients, though all patients maintained therapeutic levels of vitamin B_{12} levels (>200 ng/L) with the IN spray at all treatment visits. A limited number of subgroup analyses were completed and did not demonstrate notable results.

Patient satisfaction with the [redacted] nasal spray measured by a patient product satisfaction form appeared to be high compared to IM injections. b(4)

There was no apparent impact on homocysteine values from the [redacted] IN spray. Methylmalonic acid levels were somewhat decreased at Visit 6, and more patients showed levels in the normal range at the end of the study than at Visit 2. This finding was consistent with the overall mean increases in vitamin B_{12} levels during the study.

Safety Results:

The use of [redacted] nasal spray did not result in safety concerns in this study. Seventeen (68%) patients experienced at least one AE. The majority of AEs were judged to be unrelated to the study drug. One AE (epistaxis) was classified as possibly related to the study drug; this AE was a mild nosebleed that resolved with no action taken. One treatment-emergent serious adverse event (SAE) was reported; this SAE was a bulging L4-L5 intervertebral disc that was treated with medication and surgery. No significant safety issues were raised by AEs, vital signs, physical examinations, or clinical laboratory testing. b(4)

Name of Sponsor/Company:
Fleming & Company, Pharmaceuticals
Name of Finished Product:
——— (Cyanocobalamin, USP) Spray for Intranasal Administration
Name of Active Ingredient:
Cyanocobalamin, USP
Conclusions:
The ——— nasal spray demonstrated the ability to maintain therapeutic vitamin B_{12} levels without significant safety issues. The efficacy results in terms of B_{12} levels were robust to analysis approach (i.e., comparison to Visit 1 or therapeutic cut-off B_{12} levels). The treatment phase vitamin B_{12} levels were slightly higher than the Visit 1 B_{12} levels collected several weeks after an IM supplement injection, and all patients maintained a therapeutic level of vitamin B_{12} (>200 ng/L) at all treatment visits. Patient satisfaction with ——— spray was high as measured by a patient product assessment form, and many patients noted ——— to be preferable to IM injections. Analyses of AEs, vital signs, physical examinations, and clinical laboratory tests did not indicate significant safety issues. In total, ——— nasal spray appeared to perform safely and effectively as a replacement for IM B_{12} injection.
Date of the Report 15 June 2006

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