

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-102**

**SUMMARY REVIEW**

**MEDICAL TEAM LEADER MEMO**

**NDA#:** 22-102

**Sponsor:** Fleming & Co. Pharmaceuticals

**Drug:** CaloMist Nasal Spray (Cyanocobalamin)

**Indication:** Maintenance therapy in B12 deficient patients

**Date of Submission:** September 26, 2006

**Primary Medical Reviewer:** Hylton Joffe, M.D.

**I. Introduction and Background**

Fleming & Co. Pharmaceuticals, Inc. has submitted this 505(b)(2) application requesting approval of CaloMist™ Nasal Spray for daily maintenance therapy for vitamin B12 deficiency following stabilization of plasma B12 levels by intramuscular injections. The basis for approval is study PR99-063 which provides for the safety and efficacy, rather than bioequivalence, of CaloMist Nasal Spray.

Cyanocobalamin has been marketed in the United States since 1942. Current therapies available to treat vitamin B12 deficiency include cyanocobalamin for injection (generic formulations) and a weekly nasal spray (Nascobal, 500 mcg weekly). Oral replacement of vitamin B12 may also be effective in treating some deficient patients and is available in over-the-counter preparations. Vitamin B12 deficiency is a common cause of macrocytic (megaloblastic) anemia. In addition to affects on the hematologic system, vitamin B12 deficiency has been implicated in some neuropsychiatric conditions. Patients with neurologic signs of vitamin B12 deficiency require intramuscular administration.

**II. Clinical Efficacy**

Study PR99-063: This is a Phase 3, open-label, single-center, 8-week study evaluating 50mcg daily intranasal cyanocobalamin in patients previously maintained on monthly intramuscular B12 injections. The primary endpoint of the study was the ratio of post-treatment B12 levels relative to baseline B12 levels.

*Study population:* Subjects enrolled in the study were age 18 - 85 years who required B12 injections to maintain normal serum B12 levels. All subjects were on a stable maintenance dose of vitamin B12 with trough serum B12 levels in the normal range at the time of enrollment.

*Study treatments:* In this open-label trial, all patients received a total dose of 50 mcg cyanocobalamin daily for eight weeks, delivered as two puffs of 25 mcg cyanocobalamin - one in each nostril daily. Treatment compliance was measured by patient diary recordings.

*Efficacy measures:* Efficacy measures included serum vitamin B12 and homocysteine levels at 2, 4, 6, and 8 weeks after study drug initiation. Methylmalonic acid levels were measured at baseline and Week 8.

**Results:**

*Disposition:* A total of 30 subjects were enrolled and 25 subjects completed the study. Of the five subjects who withdrew from the study, three failed to qualify and two discontinued due to patient decision. All five subjects discontinued from the study prior to receiving study drug.

*Demographics:* The study population was comprised of 17 (68%) women and 8 (32%) men. The average age of enrollees was approximately 59 years, with a range of 27 to 82 years. The baseline mean serum vitamin B12 level was 485 ng/L with a range of 226 to 993 ng/L.

*B12 levels:* As outlined in the table below, the ratio of B12 level to baseline B12 level was greater than 1 at all time points following study drug initiation. Using the repeated analysis, the primary efficacy endpoint (the mean ratio of vitamin B<sub>12</sub> concentrations from Visits 3-6 to Visit 1) was 1.15 (90% confidence interval 1.06, 1.24), which is statistically significant (p=0.0096). Overall, 2 subjects (8%) had vitamin B12 levels of less than 200 at Day 0, which would have been the time of their next B12 IM injection. While on therapy, no subject had vitamin B12 levels less than the normal range (200 ng/L). Four subjects did have borderline vitamin B12 levels (200 – 300 ng/L) during therapy. Subgroup analyses revealed no effect of baseline vitamin B12 level, age, sex or gender on the response to study drug.

| Visit             | B12 level | Change    | Ratio to V1 | Ratio to V1                |               |
|-------------------|-----------|-----------|-------------|----------------------------|---------------|
|                   | ng/L      | ng/L      |             | Repeated Measures Analysis |               |
|                   | mean ± SD | mean ± SD | mean ± SD   | LS Mean                    | 95% CI        |
| 1, Week -2 to -4* | 484 ± 158 | ----      | ----        | ----                       | ----          |
| 2, Day 0**        | 403 ± 150 | -81 ± 89  | 0.83 ± 0.17 | 0.83                       | 0.72, 0.95    |
| 3, Week 2         | 506 ± 137 | 22 ± 125  | 1.08 ± 0.26 | 1.08                       | 0.97, 1.20    |
| 4, Week 4         | 520 ± 133 | 36 ± 153  | 1.14 ± 0.32 | 1.14                       | 1.02, 1.25    |
| 5, Week 6         | 511 ± 162 | 26 ± 187  | 1.12 ± 0.39 | 1.12                       | 1.01, 1.23    |
| 6, Week 8         | 568 ± 194 | 84 ± 222  | 1.25 ± 0.47 | 1.25                       | 1.14, 1.36    |
| Average V3-V6,    | 526 ± 143 | 42 ± 161  | 1.15 ± 0.33 | 1.15                       | 1.06, 1.24*** |

\* Week -2 to -4 = 2 – 4 weeks after B12 IM injection (midpoint of the maintenance interval)  
 \*\* Day 0 = 2 – 4 weeks after screening, coincides with when the next IM injection is due  
 \*\*\* p = 0.0096

As outlined in Dr. Joffe’s review, 12/25 subjects did not have confirmatory documentation of their last B12 injection. In that subset of patients, mean B12 levels were higher at baseline and throughout the study. However, the general response to the nasal spray drug administration were similar.

*Homocysteine levels:* Homocysteine is a metabolite in the methylation reaction cycle of methionine. In the absence of vitamin B12, homocysteine will accumulate and increased levels (> 14 μmol/L) are informative for the diagnosis of mild or subclinical vitamin B12 deficiency. In general, mean homocysteine levels fell during therapy with study drug (see table below).

| Visit             | Homocyst level | Change      | Ratio to V1 | High level |
|-------------------|----------------|-------------|-------------|------------|
|                   | mean ± SD      | mean ± SD   | mean ± SD   | n (%)      |
| 1, Week -2 to -4* | 9.52 ± 3.85    | ----        | ----        | 3 (12)     |
| 2, Day 0**        | 9.71 ± 3.99    | 0.19 ± 3.30 | 1.05 ± 0.24 | 2 (8)      |

|  |             |              |             |        |
|--|-------------|--------------|-------------|--------|
| 3, Week 2  | 9.39 ± 3.69 | -0.13 ± 3.27 | 1.02 ± 0.26 | 3 (12) |
| 4, Week 4  | 9.31 ± 4.28 | -0.21 ± 3.03 | 0.99 ± 0.22 | 2 (8)  |
| 5, Week 6  | 9.69 ± 3.93 | 0.17 ± 3.15  | 1.04 ± 0.23 | 2 (8)  |
| 6, Week 8  | 9.08 ± 3.39 | -0.44 ± 3.32 | 0.99 ± 0.25 | 1 (4)  |
| Average V3-V6,   | 9.37 ± 3.64 | -0.15 ± 2.96 | 1.01 ± 0.21 |        |
| * Week -2 to -4 = 2 - 4 weeks after B12 IM injection                                     |             |              |             |        |
| ** Day 0 = 2 - 4 weeks after screening, coincides with when the next IM injection is due |             |              |             |        |

**Methylmalonic acid levels:** Similar to homocysteine, methylmalonic acid (MMA) is a byproduct of normal cellular metabolism. In B12 deficiency, MMA levels accumulate. MMA levels > 270 nmol/L are again informative for the diagnosis of mild or subclinical vitamin B12 deficiency. MMA levels were evaluated only at Visits 2 and 6. At Visit 2, the mean MMA level was 236.8 ± 112.96 nmol/L. Overall, the mean level decreased by Visit 6 (203.6 ± 99.52 nmol/L). Eight (35%) subjects had high MMA levels at Visit 2. This number decreased to 4 (15%) by Visit 6. When evaluated as a shift in levels, 17 (68%) of subjects had no change in classification, 5 (20%) subjects shifted from High MMA levels at Visit 2 to Normal levels at Visit 6 and one subject (4%) shifted from a Normal level at Visit 2 to a High level at Visit 6.

**Conclusions:** Treatment with CaloMist (cyanocobalamin) nasal spray 50 mcg daily (one 25 mcg spray in each nostril) was effective at maintaining vitamin B12 levels in patients with vitamin B12 deficiency previously normalized on IM B12 injections. No data is available to evaluate the efficacy of this B12 preparation for the treatment of B12 deficiency in patients previously untreated.

### III. Clinical Safety

Cyanocobalamin has been marketed in the United States since 1942 and the safety of cyanocobalamin is well established. While the excipient profile for this drug product differs from that of the currently available B12 nasal spray agent, it is almost identical to the currently available over-the-counter OCEAN premium nasal spray product (see table below). Therefore, the adverse event profile of the study drug in Study PR99-063 as well as the postmarketing adverse event reporting for both cyanocobalamin products and OCEAN Premium Nasal Spray were evaluated in the safety review.

| Comparison of OCEAN Premium Saline Nasal Spray and CaloMist Nasal Spray |               |          |
|---|---------------|----------|
| Ingredient  | Amount (wt %) |          |
|   | OCEAN Premium | CaloMist |
| <b>Drug Substance</b>   |               |          |
| Cyanocobalamin, USP   |               | 0.025    |
| <b>Excipients</b>   |               |          |
| Sodium Chloride, USP  |               |          |
| Monobasic Sodium Phosphate, USP   |               |          |
| Benzyl Alcohol, NF  |               |          |
| Sodium Hydroxide, NF  |               |          |
| Benzalkonium Chloride, NF   |               |          |
| Purified Water, USP   |               |          |
| <b>Total</b>  | 100.000       | 100.000  |

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Study PR99-063:

*Disposition and exposure:* All 25 subjects who received study drug completed the trial. Overall, 96% of subjects took 80 – 100% of their prescribed dose of 50 mcg daily. In one subject, the dose of study drug was increased to 100mcg daily.

*Deaths, serious adverse events, and adverse events leading to withdrawal:* No deaths during this 8-week study. There was one serious adverse event reported – a 51 year-old woman was diagnosed with intervertebral disc protrusion on Day 52. She was treated with surgery and subsequently completed the study. There were no adverse events leading to withdrawal during this 8-week study..

*Adverse events:* Overall, seventeen (68%) subjects reported at least one adverse event. The most common adverse events were nasopharyngitis, arthralgia, dizziness, headache, and rhinorrhea – each were reported by three (12%) subjects. Adverse events reported by two (8%) subjects included pain, bronchitis, pain in extremity, nasal discomfort, and rash. No new safety signals were noted in this small trial.

*Laboratory evaluations:* Hematology parameters were the only laboratory safety assessments performed. A complete blood count was assessed at Visits 1 and 6. As outlined in Dr. Joffe's review, there were no clinical relevant changes in hematology parameters.

*Vital Signs:* There were no clinically significant changes in vital signs, which were assessed at Visits 1 and 6, in this study.

Cyanocobalamin Postmarketing Reports: As outlined in his review, Dr. Joffe identified several postmarketing reports of angioedema and angioedema-like events occurring with cyanocobalamin use. I agree with him that these events should be added to the cyanocobalamin labels.

OCEAN Premium Nasal Spray Postmarketing Reports: OCEAN® Premium Saline Nasal Spray has been manufactured and marketed for more than three decades, as a non-sterile, non-medicated isotonic aqueous moisturizing nasal spray. As outlined in the table below, there have been a very small number of patient complaints of adverse reactions (0.0001%). The most common adverse reactions are nasal irritation and allergic symptoms.

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*Conclusions:* No new safety signals were identified in this small, short study using CaloMist nasal spray. With over 60 years of experience, the safety of cyanocobalamin is well established. The safety of the product's excipients is obtained from postmarketing adverse event data of OCEAN premium nasal spray and appears to be very safe.

#### **IV. Pharmacology/Toxicology**

There are no new Pharmacology / Toxicology data submitted in this NDA. As outlined in Dr. Davis-Bruno's review, cyanocobalamin has been extensively characterized in nonclinical as well as clinical studies which are documented in literature. Currently, nonclinical studies have not been submitted for this application and are not needed based on the extensive understanding of the pharmacology and toxicology of cyanocobalamin; the active drug substance. The excipients used in the CaloMist formulation have been used previously in approved nasal products in concentrations that exceed those in CaloMist.

#### **V. Clinical Pharmacology**

As outlined in Dr. Chung's review, the clinical pharmacology package is acceptable. The basis for approval is the clinical efficacy of the nasal spray product, as assessed by vitamin B12 levels. Overall, the validation of assay methods was acceptable.

#### **VI. CMC**

As outlined in Dr. Fraser's summary basis of approval, the drug substance and drug product are both acceptable and approval is recommended.

#### **VII. Other Regulatory Requirements**

##### **VIIa. Financial Disclosure**

Dr. Joffe has reviewed financial disclosure statements submitted by the applicant and has found no apparent conflict of interest.

##### **VIIb. Pediatrics**

The Sponsor requests and should be granted a full waiver of pediatric studies.

##### **VIIc. Clinical Audits/Inspections**

A DSI audit was not conducted for this submission.

#### **VIII. Conclusions and Recommendations**

##### **VIII.a. Conclusions**

Treatment with CaloMist (cyanocobalamin) nasal spray 50 mcg daily (one 25 mcg spray in each nostril) was effective at maintaining vitamin B12 levels in patients with vitamin B12 deficiency previously normalized on intramuscular B12 injections. No data is available to evaluate the efficacy of this B12 preparation for the treatment of B12 deficiency in naïve patients. For this reason, this product should only be approved for use as maintenance therapy in patients with

normalized B12 levels. Patients who are switched from IM cyanocobalamin to CaloMist nasal spray should be monitored. If they are not maintaining adequate B12 levels, dosing should be adjusted. One subject in the trial required an increase in their CaloMist daily dose from 50 mcg to 100 mcg.

No new safety signals were identified in the clinical study conducted. With over 60 years of experience, the safety of cyanocobalamin is well established. The safety of the product's excipients is obtained from postmarketing adverse event data of OCEAN premium nasal spray and appears to be very safe.

I agree with Drs. Joffe, Fraser, Chung and Davis-Bruno that CaloMist Nasal spray can be approved for maintenance therapy in vitamin D deficient patients previously treated with cyanocobalamin injections.

**VIIIb. Recommendation**

**Approve, pending the company's agreement of the labeling revisions**

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