CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-102

PHARMACOLOGY REVIEW(S)

6/7/07

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-102**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**0606/07**
PRODUCT:	[redacted]
INTENDED CLINICAL POPULATION:	[redacted] b(4)
SPONSOR:	**Fleming**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION:	**Division of Metabolism & Encrocrinology Drugs**
PHARM/TOX REVIEWER:	**Davis-Bruno**
PHARM/TOX SUPERVISOR:	**Davis-Bruno**
DIVISION DIRECTOR:	**Parks**
PROJECT MANAGER:	**J. Johnson**

Date of review submission to Division File System (DFS): 6/7/07

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approval (AP)

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling: none

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Cyanocobalamin has been extensively characterized in nonclinical as well as clinical studies which are documented in literature. Currently, Nascobal nasal gel (NDA 19-722) and spray (NDA 21-642) are marketed forms of cyanocobalamin for this indication. Cobalamist nasal spray represents another intranasal spray formulation. 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 [redacted] formulation have been used previously in approved nasal products in concentrations that exceed those in [redacted] The excipients used in [redacted] comprise the nasal hydration spray available OTC as Ocean Premium Saline Nasal Spray.

B. Pharmacologic activity: Cyanocobalamin is a synthetic form of vitamin B12 and has equivalent pharmacologic activity.

C. Nonclinical safety issues relevant to clinical use: none

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-102
Review number: 1
Sequence number/date/type of submission: 000; Oct. 2006
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Fleming
Manufacturer for drug substance: Fleming

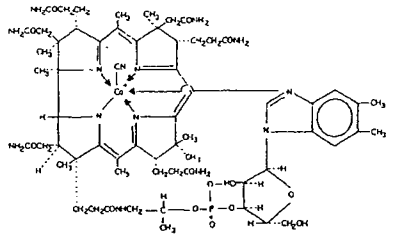
Reviewer name: Davis-Bruno
Division name: **DMEP**
HFD #: 510
Review completion date: 6/6/07

Drug:

Trade name: [redacted] nasal spray b(4)
Generic name: cyanocobalamin

Chemical name: Chemical name: 5,6-dimethyl-benzimidazolyl cyanocobamide.
CAS registry number: 68-19-9
Mole file number: N/A
Molecular formula/molecular weight: $C_{63}H_{88}CoN_{14}O_{14}P$/1355.39

Structure:



Relevant INDs/NDAs/DMFs: NDA 21-642 Nascobal nasal spray ; 19-722 Nascobal nasal gel

Drug class: vitamin B12 analogue

Intended clinical population: [redacted] b(4)

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Clinical formulation:

Table 2.6.6-1. Excipients in [redacted] Nasal Spray		
Name	Purpose	Amount Delivered in Each Spray
Sodium Chloride, USP		
Sodium Phosphate, monobasic, [redacted] USP		
Benzyl Alcohol, NF		
Sodium Hydroxide, NF		
Benzalkonium Chloride, [redacted] NF		
Purified Water, USP		

b(4)

This formulation delivers 25 µg cyanocobalamin /0.1 ml in each nostril daily (total 50 µg/day).

Route of administration: intranasal

Disclaimer: Tabular and graphical information are constructed by the sponsor unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval are owned by or are data for which Fleming has obtained a written right of reference. Any information or data necessary for approval of that Fleming does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Fleming does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval.

Studies reviewed within this submission: none submitted

Studies not reviewed within this submission: **N/A**

Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Cyanocobalamin is the most widely used and stable form of vitamin B12. The synthetic form has hematopoetic activity identical to liver extract containing stored endogenous vitamin B12.

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

Vitamin B12 is stored bound to plasma proteins in the liver. It is excreted in bile and undergoes enterohepatic recycling. Absorbed vitamin B12 is transported via transcobalamin I and II to various tissues. The diet supplies 4-15 µg/day of vitamin B12 in a protein bound form that is available for absorption after normal digestion. Vitamin B12 is bound to intrinsic factor during transit through the stomach, separation occurs in the terminal ileum in the presence of calcium ions. Vitamin B12 then enters the mucosal cell for absorption.

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

2.6.6.2 Single-dose toxicity

2.6.6.3 Repeat-dose toxicity

2.6.6.4 Genetic toxicology

2.6.6.5 Carcinogenicity

2.6.6.6 Reproductive and developmental toxicology

2.6.6.7 Local tolerance

2.6.6.8 Special toxicology studies

2.6.6.9 Discussion and Conclusions

Three nasal irritation studies in rabbits are described by the sponsor as being part of the Summary Basis of Approval (SBA) for Nascobal gel (NDA 19-722). A summary of this data has been provided by Fleming. The toxicology data indicate that up to 750 µg of cyanocobalamin BID for 15 days was administered to one nostril of the rabbits (the other nostril serves as a control). All animals survived the 15 day study. When Nascobal was given 200 µg BID for 14 days and 750 µg for 15 days and 750 µg BID (1500 µg) for 15 days, significant evidence of local irritation at the site of application or systemic toxicity was not observed.

The sponsor has provided a summary of published literature and approved uses of the excipients contained in ——— nasal spray. b(4)

Sodium chloride is an inactive ingredient in several inhalant (IH) and intranasal (IN) products. ——— contains sodium chloride at ——— which is below the approved range for nasal products. b(4)

Table 2.6.6-2. Sodium Chloride Approvals

Route	Dosage Form	Maximum Potency
Inhalation	Inhalant	Not reported
Inhalation	Solution	3.16%
Inhalation	Solution for inhalation	Not reported
Nasal	Solution	0.668%
Nasal	Spray	0.9%
Nasal	Spray metered	1.9%
Respiratory (inhalation)	Solution	2.7%
Respiratory (inhalation)	Solution, aerosol for inhalation	1.125%
Respiratory (inhalation)	Solution for inhalation	2.7%

Source: CDER Inactive Ingredient Database, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, information retrieved August 22, 2006

Sodium phosphate is extensively used in pharmaceuticals as a ——— agent. It is present as an inactive ingredient in several IN products. ——— contains sodium phosphate at ——— which is within the approved range for products given by an IN route. b(4)

Table 2.6.6-3. Sodium Phosphate Approvals			
Type	**Route**	**Dosage Form**	**Maximum Potency**
Sodium phosphate	Nasal	Solution	0.189%
Sodium phosphate, dibasic	Nasal	Spray	Not reported
Sodium phosphate, dibasic, anhydrous	Nasal	Spray	0.011%
Sodium phosphate, dibasic, dihydrate	Nasal	Spray, metered	0.3%
Sodium phosphate, dibasic, dodecahydrate	Nasal	Spray, metered	14.3%
Sodium phosphate, dibasic, heptahydrate	Nasal	Solution	0.0452%
Sodium phosphate, dibasic, heptahydrate	Nasal	Spray, metered	0.486%
Sodium phosphate, monobasic, dihydrate	Nasal	Spray, metered	4.2%

Source: CDER Inactive Ingredient Database, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, information retrieved August 22, 2006

2.6.6.3.3 Benzyl Alcohol

Benzyl alcohol is used in a wide variety of cosmetic and pharmaceutical products as a preservative. Although at certain levels benzyl alcohol has known toxic effects, an acceptable daily intake has been established at 5 mg/kg by the World Health Organization (Nair, 2001), which is almost — orders of magnitude above the benzyl alcohol intake from a daily dose of ——— (about ——— assuming a body weight of 50 kg). A search of the CDER Inactive Ingredient Database revealed that benzyl alcohol is found as an inactive ingredient in a nasal solution with a maximum potency of 0.5% compared to ———

b(4)

b(4)

Table 2.6.6-4. Benzyl Alcohol Approvals		
Route	**Dosage Form**	**Maximum Potency**
Nasal	Solution	0.5%

Source: CDER Inactive Ingredient Database, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, information retrieved August 22, 2006

Literature is provided by the sponsor on clinical (adult, pediatric) and animal acute inhalational studies with benzyl alcohol as well as parenteral, oral and peritoneal administration. These studies are supportive but do not directly address the route and chronic use proposed here. Since the levels of benzyl alcohol are lower than those utilized in prior approved products by the IN route of administration the proposed levels are considered adequately characterized for safety.

Benzalkonium chloride is an antimicrobial agents used at concentrations up to 0.1% in other approved IN and IH products. Cobalamist contains — benzalkonium chloride which is ——— lower than in other approved nasal products.

b(4)

Table 2.6.6-7. Benzalkonium Chloride Approvals		
Route	**Dosage Form**	**Maximum Potency**
Inhalation	Solution	20%
Nasal	Gel	Not reported
Nasal	Solution	1%
Nasal	Spray	0.119%
Nasal	Spray, metered	0.1176%
Source: CDER Inactive Ingredient Database, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, information retrieved August 22, 2006		

Sodium hydroxide is used in several inhaled or IN products the drug product. It is present in negligible amounts and hence is usually listed as below the level of quantitation in other products administered IN. b(4)

Table 2.6.6-6. Sodium Hydroxide Approvals		
Route	**Dosage Form**	**Maximum Potency**
Inhalation	Aerosol, metered	Not reported
Inhalation	Solution	8%
Nasal	Solution	Not reported
Nasal	Spray	Not reported
Nasal	Spray, metered	Not reported
Respiratory (inhalation)	Powder, for inhalation	Not reported
Respiratory (inhalation)	Solution, aerosol, for inhalation	Not reported
Respiratory (inhalation)	Solution, injection	Not reported
Source: CDER Inactive Ingredient Database, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, information retrieved August 22, 2006		

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Cyanocobalamin is a synthetic form of vitamin B12. It is the most stable and widely used form of vitamin B12. It is absorbed from the diet in the terminal ileum and is transported to the peripheral tissues by binding to transcobalamin. Parenteral administration of cyanocobalamin completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency. The degree of improvement depends on the duration and severity of the lesions although the progression of lesions is immediately arrested. Intrinsic factor deficiency results in pernicious anemia.

The Summary Basis of Approval for Nascobal contained nasal irritation studies in rabbit. These data indicate that up to 1500 µg/day of cyanocobalamin for 15 days was administered to one nostril of the rabbits. All animals survived the 15 day study. significant evidence of local irritation at the site of application or systemic toxicity was not observed.

Cyanocobalamin is approved for marketing in an intranasal spray, and gel. The excipients in both of these formulations are identical except for the absence of the methylcellulose in the gel formulation. In the marketed as well as this proposed product the excipients are present at levels at or below those listed in the FDA Inactive Ingredient Guide in other approved intranasal products. The excipients used in the ——— nasal spray are used in other approved intranasal products in some cases at higher levels. The excipient components of ——— nasal spray are identical to the marketed OTC product Ocean Premium Nasal Spray. b(4)

Based on the documented mechanism of action and safety of cyanocobalamin in published literature as well as the safety information available for the excipients being used in the drug product it is reasonably safe to approve this product for marketing. There are no outstanding nonclinical safety issues to address and therefore nonclinical studies are not required or needed.

Unresolved toxicology issues (if any): none

Recommendations: approval

Suggested labeling: The proposed labeling in sections: 8. Use in specific population, 12.1 Mechanism of action and 13. Nonclinical toxicology are identical to that in the last approved Nascobal nasal spray label and are therefore acceptable as written.

APPENDIX/ATTACHMENTS N/A

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/s/

Karen Davis-Bruno
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PHARMACOLOGIST