CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-642

PHARMACOLOGY REVIEW(S)

P/T consult Ok
6-28-04

NDA 21-642

Signed off in DFS on 6/28/04

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-642
Review Number: 1

Sequence number/date/type of submission: December 26, 2003 (original application). It is a It is a 505(b)(1) application
Information to sponsor: Yes ( ) No (X)

Sponsor: Nastech Pharmaceuticals company, Inc., Hauppauge, NY.

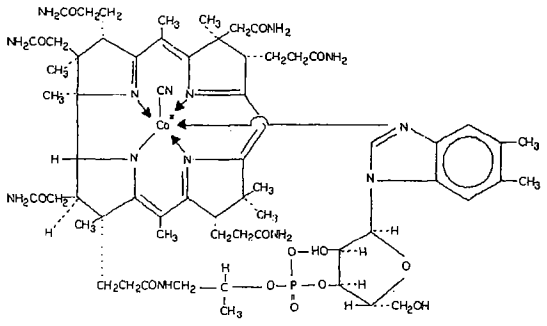
Manufacturer for drug substance: The manufacturer of the drug substance (cyanocobalamin, USP) is —

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrine Drug products, **HFD #:** 510
Review completion date: 6/25/2004

Drug:

Trade name: Nascobal (Cyanocobalamin, USP) spray for intranasal administration, 500 µg/0.1ml.
Generic name (list alphabetically): Cyanocobalamin
Code name: Nascobal (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 19-722 (Nascobal nasal gel, cyanocobalamin, USP for intranasal administration) & IND 25, 696 (Nascobal nasal spray). DMF numbers —

Drug class: It is a synthetic form vitamin B12 with equivalent vitamin B12 activity.

Indication: It is indicated for maintenance of normal hematologic status in patients with pernicious anemia.

Clinical formulation: Each bottle contains 2.3 ml of a 500 µg/0.1 ml of cyanocobalamin solution

Route of administration: Intranasal spray

Proposed use: The drug is indicated for maintenance of normal hematologic status in patients with pernicious anemia, who are in remission following intramuscular vitamin B12 therapy, and who have no nervous system invovement. This drug is also indicated for other vitamin B12 deficiencies including dietary deficiency of vitamin B12 in strict vegetarians or in AIDS or patients with Crohn's disease, in whom the mal-absorption of vitamin B12 may result due to structural or functional damage to stomach or due to inadequate secretion of intrinsic factor or due to gastric atrophy (gastrectomy, certain malignancies). The recommended dose of the intranasal spray is 500 µg administered once weekly.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: Indication and previous studies

Executive Summary

1. Recommendations

A. **Recommendation on approvability**
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:
The preclinical studies are adequate to support the recommended doses up to 500 µg/once weekly. No further pre-clinical studies are required

C. **Recommendation on Labeling: No changes in** labeling section are required as the label for this nasal spray product is similar to approved nasal gel (NDA 21-722)

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies
Nascobal (Cyanocobalamin, USP) gel for intranasal administration (500 ug/0.1ml) is an approved drug in USA (NDA 19-722). Since extensive nonclinical studies have been conducted with the approved Nascobal gel, no additional toxicity studies are considered necessary with the current nasal spray drug product.

B. Pharmacologic activity
Cyanocobalamin is a synthetic form of vitamin B12 and has equivalent vitamin B12 activity. Administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency.

C. Nonclinical safety issues relevant to clinical use
There are no new nonclincal safety issues relevant to the clinical use with the current drug product, except the ones already discussed in NDA 19-722 for approved intranansal gel.

III. Administrative

A. Reviewer signature: ----------

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21642 (nascobal/vitamin-B12 nasal spary)

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

Cyanocobalamin is a synthetic form of vitamin B12 with vitamin B12 activity. It is the most stable and widely used form of vitamin B12 and has hematopoietec activity apparently identical to that of the antianemia factor in purified liver extract. Vitamin B12 is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection. It is bound to plasma proteins and stored in the liver. It is excreted in the bile and undergoes some enterohepatic recycling. Absorbed vitamin B12 is transported via specific B12 binding proteins, transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B12 storage. The intramuscular administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency; and prevents progression of neurologic damage.

The average diet supplies about 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 in the terminal ileum in the presence of calcium ions, and vitamin B12 enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount is absorbed (1%) by simple diffusion. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in mal-absorption of vitamin B12. This vitamin is present in abundance in food of animal origin, but is not present in foods of plant origin.

The parenteral administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency, the degree of improvement depends on the duration and severity of lesions, although progression of the lesions is immediately arrested. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of spinal cord, therefore prompt intramuscular (IM) administration of vitamin B12 prevents progression of neurologic damage

Nascobal or Cyanocobalamin USP is currently a marketed drug in US, as a nasal gel (NDA 19-722). The recommended doses of intranasal gel are 500 µg/day.

The nasal spray pump used for NDA 21-642 Nascobal Spray is manufactured by —— (DMF —, DMF — has been previously reviewed and found adequate for ANDA ——

The current sponsor (Nastech Pharmaceuticals) has come up with the new formulation of the drug, which they claim has bioavailability greater than that of the gel form. The current sponsor refers to the previously approved nascobal gel (NDA 19-722) and intramuscular formulation.

The Clinical formulation that contains the active drug and inactive ingredients in the approved nasal gel and new nasal spray are shown below:

Table. Composition of Nascobal gel and spray:

Drug Product

Nascobal® Nasal Spray is a line-extension of the commercial product Nascobal® Gel for Intranasal Administration. Nascobal® Nasal Spray is reformulated without methylcellulose (

The clinical trial formulation is identical to the proposed commercial formulation.

Table P.2-1: Composition of Nascobal® Gel versus Nasal Spray

Ingredient	Nasal Gel Quantity (g/100 g)	Nasal Spray Quantity (g/100 g)
Cyanocobalamin, USP		0.50
Citric Acid, USP		
Sodium Citrate, USP		
Methylcellulose, USP		none
Glycerin, USP		
Benzalkonium Chloride Solution, NF		
Purified Water, USP q.s.		

Cyanocobalamin is prepared by

The drug is soluble parts in water. Cyanocobalamin is hygroscopic and light sensitive and stable between pH 4.5-5.0.

Cyanocobalamin spray contains five compendial inactive ingredients, all five excipients used here have been used at the recommended or higher doses in other approved products in the FDA inactive ingredient guide, 1996. Both gel and spray formulations are made in the same facility, except the nasal spray contains methylcellulose, which is and is omitted from the spray formulation.

Since non-clinical studies have been conducted with the approved gel drug product (under NDA 19-722), no additional non-clinical studies have been considered necessary, and have not been provided for the current drug (spray formulation).

X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

Cyanocobalamin is a synthetic form of vitamin B12 with vitamin B12 activity. Nascobal or Cyanocobalamin USP is currently a marketed drug in US, as a nasal gel (NDA 19-722). The recommended doses of intranasal gel are 500 µg/day. The current drug Nascobal (Cyanocobalamin USP) spray is basically the same product as the gel except the spray is reformulated without methylcellulose (

Since the spray is a new dosage form (i.e. with FDA

recommended (on 11/1/2001) submission of a new NDA, as well as a bioequivalence study to compare IM injection, nasal gel and nasal spray under existing IND 25,696.

The proposed indication for Nascobal nasal spray is identical to that of Nascobal gel

It is available in dosages of 500 ug/0.1 ml. As per labeling, recommended doses of both gel or spray are 500 ug [redacted]

No pharm/tox studies are available from NDA 19-722, except a 15-day study in rabbits showing lack of irritation and lack of nasal histopathology at 160 fold the human dose, based on body surface area. Sponsor states that over the last 8 years the clinical experience with this drug is consistent with the lack of local or systemic toxicity in animal studies.

Sponsor quotes a couple of references and state that there are no known reports which attribute carcinogenic or mutagenic properties to cyanocobalamin. It also does not pose any teratogenic potential. Vitamin B12 is Generally Recognized as Safe (GRAS) Substance.

As per label, the long term studies in animals to evaluate the carcinogenic potential have not been done. There is no evidence from long term use in patients with pernicious anemia that vitamin B12 is carcinogenic.

Nascobal is labeled as pregnancy category 'C'. No animal reproduction studies have been conducted with vitamin B12. It is not known if vitamin B12 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, vitamin B12 is an essential vitamin and requirements are increased during pregnancy

The bioequivalence (BE) study was conducted to compare the PK profile of a single intra-nasally-administered spray vs approved gel (Nascobal, using 500 µg/day dose of each) vs intramuscular injection of vitamin B12 (100 µg/day) in a fasted state in normal healthy male and female subjects (study C02-016). This study showed that AUC values were comparable with the two formulations (191 with spray vs 186 pg.h/ml with the gel). Thus, relative bioavailability (BA) of spray was 1.04 vs the gel. In contrast, the relative BA of spray vs the IM injection was 0.61, and gel vs injection was 0.63. Additionally using weekly intranasal spray vs the monthly injection of the drug prevents excessive spikes seen with the injection.

Safety Evaluation: It is an approved drug under NDA 19-722. Supportive information for excipients in Nascobal nasal spray is provided. Only difference in the current drug product is that it is a nasal spray vs the approved drug (NDA 19-722) which is a nasal gel. As per labeling, recommended doses of both gel or spray are 500 µg/ [redacted]

Labeling Review: The preclinical sections of the label for this product (spray) are similar to the approved Nascobal label (NDA 19-722, the intranansal gel). Therefore, no changes in the label are required with the current spray formulation.

External Recommendation: From the preclinical standpoint, approval of this application is recommended.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21642 (nascobal vitamin B12 nasal spray)

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

/s/

Indra Antonipillai
6/28/04 03:54:15 PM
PHARMACOLOGIST
From the pharm/tox standpoint, this application is recommended for approval
This application is recommended for approval

Karen Davis-Bruno
6/28/04 03:59:10 PM
PHARMACOLOGIST
concur with recommendations

02/09/04

NDA 21-642

Review completed:
Signed off in DFS on

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-642
Review Number: 1

Sequence number/date/type of submission: December 26, 2003 (original application). It is a It is a 505(b)(1) application
Information to sponsor: Yes ( ) No (X)

Sponsor: Nastech Pharmaceuticals company, Inc., Hauppauge, NY.

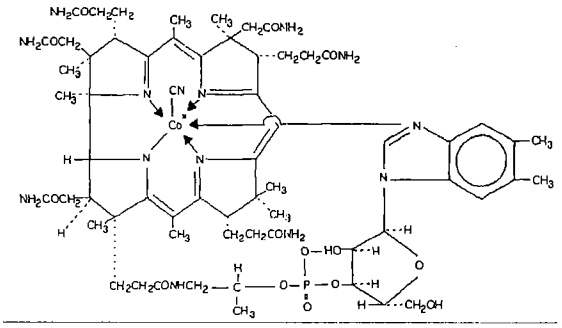
Manufacturer for drug substance: The manufacturer of the drug substance (cyanocobalamin, USP) is

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrine Drug products, **HFD #:** 510
Review completion date: 1/22/2004

Drug:

Trade name: Nascobal (Cyanocobalamin, USP) spray for intranasal administration, 500 ug/0.1ml.
Generic name (list alphabetically): Cyanocobalamin
Code name: Nascobal (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 19-722 (Nascobal nasal gel, cyanocobalamin, USP for intranasal administration) & IND 25, 696 (Nascobal nasal spray). DMF numbers —

Drug class: It is synthetic vitamin B12.

Indication: It is indicated for maintenance of normal hematologic status in patients with pernicious anemia.

Clinical formulation: Each bottle contains 2.3 ml of a 500 µg/0.1 ml of cyanocobalamin solution

Route of administration: Intranasal spray

Proposed use: The drug is indicated for maintenance of normal hematologic status in patients with pernicious anemia, who are in remission following intramuscular vitamin B12 therapy, and who have no nervous system invovement. This drug is also indicated for other vitamin B12 deficiencies including dietary deficiency of vitamin B12 in strict vegetarians or in AIDS patients or Crohn's didease patients where malaabsorption of vitamin B12 may result due to structural or functional damage to stomach or due to inadequate secretion of intrinsic factor or due to gastric atrophy (gastrectomy, certain malignancies). The recommended dose of the intranasal spray is 500 µg administered once weekly.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: None

Executive Summary

1. Recommendations

A. **Recommendation on approvability**
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:
The preclinical studies are adequate to support the recommended doses up to 500 µg/once weekly. No further pre-clinical studies are required

C. **Recommendation on Labeling:** see the labeling section on page 22 to 25

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies
Nascobal (Cyanocobalamin, USP) gel for intranasal administration (500 ug/0.1ml) is an approved drug in USA as — (NDAs 19-722). Since extensive nonclinical studies have been conducted with the approved Nascobal, no additional toxicity studies are considered necessary with the current nasal spray drug product.

B. Pharmacologic activity
Cyanocobalamin is a synthetic form of vitamin B12 and has equivalent vitamin B12 activity. The intaramuscular administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency.

C. Nonclinical safety issues relevant to clinical use
There are no new nonclincal safety issues relevant to the clinical use with the current drug product, except the ones already discussed in NDA 19-722 for approved of intranansal gel.

III. Administrative

A. Reviewer signature: ----------

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21656 (Tricor EZ)

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

Cyanocobalamin is a synthetic form of vitamin B12 with vitamin B12 activity. It is the most stable and widely used form of vitamin B12 and has hematopoitec activity apparently identical to that of the antianemia factor in purified liver extract. Vitamin B12 is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection. It is bound to plasma proteins and stored in the liver. It is excreted in the bile and undergoes some enterohepatic recycling. Absrobed vitamin B12 is transported via specific B12 binding proteins, transcobalamin I and II, to te various tissues. The liver is the main organ for vitamin B12 storage. The intaramuscular administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency; and prevents progression of neurologic damage.

The average diet supplies about 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 in the terminal ileum in the presence of calcium ions, and vitamin B12 enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount is absorbed (1%) by simple diffusion. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in mal-absorption of vitamin B12. This vitamin is present in abundance in food of animal origin, but is not present in foods of plant origin.

The parenteral administration of Cyanocobalamin (or vitamin B12) completely reverses the megablastic anemia and GI symptoms of vitamin B12 deficiency, the degree of improvement depends on the duration and severity of lesions, although progression of the lesions is immediately arrested. Intreinsic factor deficiency causes prrnicious anemia, which ma be associated with subacute combined degeneration of spinal cord, therefore prompt IM administration of vitamin B12 prevents progression of neurologic damage

Nascobal or Cyanocobalamin USP is currently a marketed drug in US, as a nasal gel (NDA 19-722). The recommended doses of intranasal gel are 500 µg/day.

The current sponsor (Nastech Pharmaceuticals) has come up with the new formulation of the drug, which they claim has bioavailability greater than that of the gel form. The current sponsor refers to the previously anascobal gel (NDA 19-722) and intramuscular formulation.

The Clinical formulation that contain the active drug and following inactive ingredients in the approved nasal gel and new nasal spray are shown below:

Table. Composition of Nascobal gel and spray:

Drug Product

Nascobal® Nasal Spray is a line-extension of the commercial product Nascobal® Gel for Intranasal Administration. Nascobal® Nasal Spray is reformulated without methylcellulose

The clinical trial formulation is identical to the proposed commercial formulation.

Table P.2-1: Composition of Nascobal® Gel versus Nasal Spray

Ingredient	Nasal Gel Quantity (g/100 g)	Nasal Spray Quantity (g/100 g)
Cyanocobalamin, USP		0.50
Citric Acid, USP		
Sodium Citrate, USP		
Methylcellulose, USP		none
Glycerin, USP		
Benzalkonium Chloride Solution, NF		
Purified Water, USP q.s.		

Cyanocobalamin is prepared by

The drug is soluble parts in water. Cyanocobalamin is hygroscopic and light sensitive and stable between pH 4.5-5.0.

Cyanocobalamin spray contains five compendial inactive ingredients, all five excipients used here have been used at the recommended or higher doses in other approved products in the FDA inactive ingredient guide, 1996. Both gel and spray formulations are made in the same facility, except the nasal spray

Since non-clinical studies have been conducted with the approved drug (under NDA 19-722), no additional non-clinical studies have been considered necessary, and have not been provided for the current drug (spray formulation).

X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

Cyanocobalamin is a synthetic form of vitamin B12 with vitamin B12 activity. Nascobal or Cyanocobalamin USP is currently a marketed drug in US, as a nasal gel (NDA 19-722). The recommended doses of intranasal gel are 500 µg/day. The current drug Nascobal (Cyanocobalamin USP) spray is basically the same product as the gel except the spray is reformulated without methylcellulose (

Since the spray is a new dosage form (i.e. with

), FDA recommended (on 11/1/2001) submission of a new NDA, as well as a bioequivalence study to compare IM injection, nasal gel and nasal spray under existing IND 25,696.

The proposed indication for Nascobal nasal spray is identical to that of Nascobal gel

It is available in dosages of 500 ug/0.1 ml. As per labeling, recommended doses of both gel or spray are 500 ug/day.

No pharm/tox studies are available from NDA 19-722, except a 15-day study in rabbits showing lack of irritation and lack of nasal histopathology at 160 fold the human dose based on body surface area

Sponsor quotes a couple of references and state that there are no known reports which attribute carcinogenic or mutagenic properties to cyanocobalamin. It also does not pose any teratogenic potential. Vitamin B12 is Generally Recognized as Safe (GRAS) Substances.

As per label, the long term studies in animals to evaluate the carcinogenic potential have not been dose. There is no evidence from long term use in patients with pernicious anemia that vitamin B12 is carcinogenic.

Nascobal is labeled as pregnancy category 'C'. No animal reproduction studies have been conducted with vitamin B12. it is not known if vitamin B12 can cause fetal harm when administered to a pregnant woman

Safety Evaluation: It is an approved drug (under NDA 19-722). Supportive information for excipients in Nascobal nasal spray is provided.

External Recommendation: From the preclinical standpoint, approval of this application is recommended.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21656 (Tricor EZ fenofibrate)

**are listed in the FDA Inactive Igredient Guide for other approved nasal spray drug products at concentrations greater than the concentration in Nascobal spray formulation

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

/s/

Indra Antonipillai
2/9/04 01:38:30 PM
PHARMACOLOGIST
From the pharm/tox point of view this application is filable
From the pharm/tox point of view this application is filable

Karen Davis-Bruno
2/9/04 01:41:01 PM
PHARMACOLOGIST