CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-642

CHEMISTRY REVIEW(S)

NDA 21-642

Nascobal®
(Cyanocobalamin, USP)
Nasal Spray

Nastech Pharmaceutical Company, Inc.

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-642
2. REVIEW #: 1
3. REVIEW DATE: Oct-07-2004
4. REVIEWER: Yvonne Yang
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Dec-20-2003
Amendment	Mar-24-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Nastech Pharmaceutical Company, Inc.
Address:	45 Davis Drive, Hauppauge, NY 11788
Representative:	Gordon Brandt, M.D.
Telephone:	631-273-0101

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nascobal® Nasal Spray
b) Non-Proprietary Name (USAN): Cyanocobalamin, USP
c) Code Name/# (ONDC only): CAS-68-19-9
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY: Vitamins other than D

11. DOSAGE FORM: Spray, metered

12. STRENGTH/POTENCY: 500 mcg/0.1 ml/actuation

13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: ___X___ Rx _____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cyanocobalamin, USP
Cobinamide cyanide phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazol inner salt
$C_{63}H_{88}CoN_{14}O_{14}P$ (Molecular Weight = 1,355.39 Da)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
/	II			3	Adequate	Sept-04-2003	Reviewed by Guoping Sun
/	III			1	Adequate	Aug-20-2004	Reviewed by Yvonne Yang
/	III			1	Adequate	Aug-13-2004	Reviewed by Yvonne Yang
/	III			1	Adequate	Sept-21-2004	Reviewed by Yvonne Yang
/	III			3	Adequate (for 5 ml)	Nov-17-2003	Reviewed by Elsbeth Chikhale

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-722	Nascobal® Gel

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall **Withhold** recommendation per EER. Facility for drug substance manufacturer — not ready for inspection.	Sept-29-2004	Yvonne Yang
Pharm/Tox	Preclinical studies are adequate to support the recommended doses up to 500 µg/once weekly. Recommendation for Approval for the proposed indication.	Jun-28-2004	Indra Antonipillai
Biopharm	Bioequivalence results unacceptable due to lack of demonstration of bioequivalence between the nasal spray and nasal gel formulations using baseline corrected analysis	Oct-01-2004	Jaya Vaidyanathan
Methods Validation	Validation of analytical methods has been reviewed and found adequate	Oct-07-2004	Yvonne Yang
ODS/DMETS	MDETS has no objection to the used of the proposed proprietary name Nascobal® Nasal Spray	Aug-04-2004	Tia Harper-Velazquez
EA	Categorical exclusion granted	Sept-21-2004	Yvonne Yang

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 21642

The Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability

NDA 21-642 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls pending an overall acceptable cGMP recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments:

Nascobal® Nasal Spray is indicated for (1) the maintenance of normal hematologic status in pernicioys anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement, and (2) a supplementation for other vitamin B_{12} deficiencies.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Nascobal® Nasal Spray is a non-sterile aqueous solution containing cyanocobalamin, USP (vitamin B_{12}) for administration as a spray to the nasal mucosa. Each carton of the drug product contains one 3-ml amber glass fill bottle and one nasal spray pump. The nasal spray pump is affixed to the 3-ml fill bottle by the pharmacist at the time the drug is dispensed. Each bottle of Nascobal® Nasal Spray contains cyanocobalamin, USP (— w/w), citric acid ___, — w/w), sodium citrate — , w/w), glycerin — w/w), benzalkonium chloride — and purified water. Each bottle is filled with 2.3 ml of the cyanocobalamin solution, and intended to deliver at least 8 doses. After initial priming, each spray of the drug product delivers an average of 0.1 ml of Nascobal® Nasal Spray containing 500 µg (per actuation per dose) of cyanocobalamin, USP.

The proposed expiry (24 months at controlled room temperature, 15-30 °C or 59-86 °F, protected from light and from freezing) for Nascobal® Nasal Spray is supported by the submitted stability data . A proposed in-use expiry for Nascobal® Nasal Spray i — when stored at controlled room temperature.

Drug Substance:

Cyanocobalamin is a synthetic form of vitamin B_{12} with equivalent vitamin B_{12} activity. It is the most stable and widely used form of vitamin B_{12}. Cyanocobalamin is very hygroscopic in its anhydrous form, light sensitive, and sparingly to moderately soluble in water. Aqueous solutions of cyanocobalamin are most stable between pH 4.5 and 5.0. The pharmacologic activity of cyanocobalamin is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (vitamin C), but not by autoclaving for short period of time (15-20 min) at 121°C. All information with respect to the chemistry and manufacturing controls of the drug substance cycanocobalamin, USP is provided by reference in — DMF —. The information provided in DMF — as been reviewed and found adequate to support a currently markedly drug product, cyanocobalamin injection USP.

B. Description of How the Drug Product is Intended to be Used

Nascobal® Nasal Spray is intended to be used for the indication of maintenance of normal hematologic status in patients with pernicious anemia and supplementation for other vitamin B_{12} deficiencies. The recommended dose is one spray of cyanocobalamin solution (500 µg/0.1 ml per actuation) administered intranasally once a week.

Each carton of Nascobal® Nasal Spray is supplied with one 3-ml amber glass bottle with a white screw-on cap and one nasal spray pump with a dust cover. Each bottle of Nascobal® Nasal Spray is filled with 2.3 ml of the cyanocobalamin solution, and is intended to deliver 8 doses. The nasal spray pump is affixed to the amber glass bottle by the pharmacist by unscrewing the white cap from the glass bottle and screwing the nasal spray pump unit tightly onto the bottle. The assembled Nascobal® Nasal Spray unit, bottle with pump attached, is re-covered with the dust cover, and returned to the carton before dispensing to the patients.

Nascobal® Nasal Spray unit must be primed properly before use to ensure the delivery of a correct dose. To prime a new unit, the patients are instructed to (1) place the nozzle between the first and the second finger with the thumb on the bottom of the bottle, (2) pump firmly and quickly until the first appearance of spray, and (3) pump an addition two times. After the new pump is primed, it is ready to use for dose 1. The unit must be re-primed before administration of dose 2 through dose 8 by pumping the unit only once immediately before each use.

The patients are instructed —

The Nascobal® Nasal Spray unit with pump attached should be kept covered in the carton, and stored upright at controlled room temperature (at 20-25 °C/68-77 °F with excursions permitted at 15-30 °C/59-86 °F), protected from light and from freezing, until ready to use. The Nascobal® Nasal Spray unit with pump attached should be discarded after the eighth dose.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-642 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls pending an overall acceptable cGMP recommendation from the Office of Compliance.

- Nascobal® Nasal Spray is a new dosage form for the currently marketed Nascobal® Gel (NDA 19-722). The formulation for Nascobal® Nasal Spray differs from that for the gel product only in the elimination of methylcellulose

- Available real time stability data for Nascobal® Nasal Spray support a proposed expiry date of 24 months at controlled room temperature.

- The new container/closure system is comparable to that of the currently approved product. The actuator chosen for Nascobal® Nasal Spray, with respect to product contact material, is identical to that used for Nascobal® Gel. The performance of the nasal spray pump is ensured by the spray characterization testing included in the regulatory specifications for Nascobal® Nasal Spray.

III. Administrative:

A. Reviewer's Signature in DFS

B. Endorsement Block in DFS

C. CC Block in DFS

56 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Yvonne Yang
10/8/04 09:38:38 AM
CHEMIST

Mamta Gautam-Basak
10/8/04 02:37:02 PM
CHEMIST
Concur

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21642/000
Org Code : 510
Priority : 3S

Sponsor: NASTECH PHARM
45 DAVIDS DR
HAUPPAUGE, NY 11788

Stamp Date : 29-DEC-2003
PDUFA Date : 02-FEB-2005
Action Goal :
District Goal: 04-DEC-2004

Brand Name : NASCOBAL(CYANOCOBALAMIN NASAL SPRAY)500M
Estab. Name:
Generic Name: CYANOCOBALAMIN NASAL SPRAY 500MG/0.1ML
Dosage Form: (SPRAY)
Strength : 500 MCG/0.1 ML

FDA Contacts:			
	H. WIELAND	Project Manager (HFD-510)	301-827-6410
	Y. YANG	Review Chemist (HFD-510)	301-827-6371
	M. GAUTAM BASAK	Team Leader (HFD-510)	301-827-9084

Overall Recommendation: ACCEPTABLE on 12-JAN-2005by S. ADAMS (HFD-322) 301-827-9051
WITHHOLD on 29-SEP-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : — FEI : —

DMF No: — AADA:

Responsibilities: —

Profile : CFN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JAN-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-JUN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

NASTECH PHARMACEUTICAL CO INC

3450 MONTE VILLA PKY

BOTHELL, WA 98021

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-JUL-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JAN-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

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/s/

Yvonne Yang
1/26/05 02:30:25 PM
CHEMIST