CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-802

CHEMISTRY REVIEW(S)

NDA 21-802

Focalin™ (dexmethylphenidate hydrochloride) Extended Release Capsules

Novartis Pharmaceuticals Corporation

Chhagan G. Tele, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-802

2. REVIEW #: 1

3. REVIEW DATE: April 11, 2005

4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-JUL-2004
Amendment N-000(BC)	30-NOV-2004
Fax	08-FEB-2005
Fax	15-FEB-2005
Fax	18-FEB-2005
Fax	16-MAR-2005
Fax	17-MAR-2005
Fax	18-MAR-2005
Fax	24-MAR-2005
Fax	29-MAR-2005
Fax	31-MAR-2005
Fax	01-APR-20045

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, East Hanover, New Jersey 07936-1080
Representative:	Mara Stiles, Senior Regulatory Director
Telephone:	(862) 778-3771

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Focalin™
b) Non-Proprietary Name (USAN): N/A

c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1); The RLD is Focalin® (dexmethylphenidate hydrochloride) Tablets, 2.5 mg, 5 mg, and 10 mg, [redacted] NDA 21-278.

10. PHARMACOL. CATEGORY: For the treatment of Attention Deficit Hyperactivity Disorder.

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 5 mg, 10 mg, 20 mg [redacted]

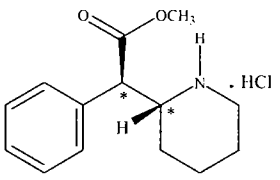
13. ROUTE OF ADMINISTRATION: Oral

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:

USAN Name (2002):	Dexmethylphenidate Hydrochloride
Non-Proprietary Name:	The chemical name is 2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride, (αR,2R)- and methyl (2R)-phenyl[(2R)-piperidin-2-yl]acetate hydrochloride. The trivial name is d-threo-methylphenidate hydrochloride
Chemical Formula:	$C_{14}H_{19}NO_2.HCl$
Molecular Weight:	269.77
CAS registry #:	19262-68-1
Structure:	

* Asymmetric carbon centers

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	01-MAR-05 Dr. Chhagan Tele	LOA 14 NOV-02
	II			3	Adequate	01-MAY-03 Dr. H.A. Hahm	LOA 14-NOV-02
	III			4	Adequate	05-SEP-01 Dr. R.Frankewich	LOA 01-JUN-04
	III			3	Adequate	26-FEB-2002 Dr. Arthur Shaw	LOA 03-OCT-03
	III			3	Adequate	26-SEP-2000 Dr. D. Klein	LOA 21-OCT-02
	III			3	Adequate	22-APR-2002	LOA 28-APR-04
	III			3	Adequate	24-MAR-2001	LOA 11-JUL-02
	III			3	Adequate	12-OCT-2000 Dr. D. Klein	LOA 16-DEC-03
	III			3	Adequate	26-SEP-2000	LOA 09-FEB-04

[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	21-278	Focalin™ Tablets
IND	63,885	Commercial IND (ADHD)

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation Acceptable	30-AUG-04	J.D. Ambrogio (HFD-322)
Pharm/Tox	Pending		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Pending		To be forwarded once specifications and methods finalized
DMETS			
EA	Acceptable, categorical exclusion granted as per information from Novartis in this NDA	As per this review	Chhagan G. Tele, Ph.D. (HFD-120)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time NDA 21-802 for Focalin™ (dexmethylphenidate hydrochloride) Extended Release Capsules is recommended **APPROVAL** from the CMC standpoint. **Based on the stability data, an 18 month expiry will be granted for Focalin XR capsules**.

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

None as per this review.

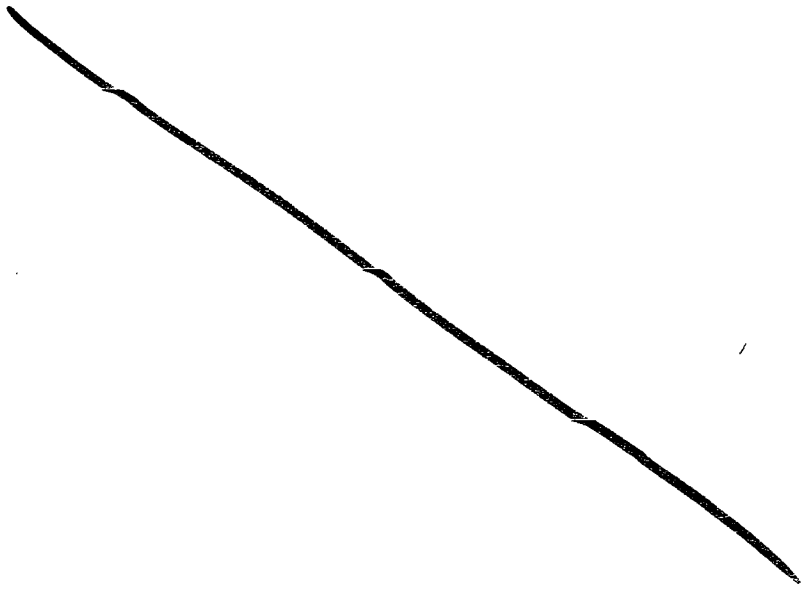
II. Summary of Chemistry Assessments

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

Focalin™ (dexmethylphenidate hydrochloride) extended release capsules are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Ritalin®, an immediate release form of racemic methylphenidate hydrochloride, has been available in the US since 1955 and is used for the treatment of ADHD in children. Focalin™ (dexmethylphenidate hydrochloride) is pharmacologically active d-threo enantiomer of Ritalin. Dexmethylphenidate hydrochloride was originally approved in 2001, under NDA 21-278, as conventional tablets (Focalin® Tablets, 2.5 mg, 5 mg, and 10 mg) manufactured and distributed by Novartis. The currently available conventional tablet (immediate release tablet) formulation of Focalin is a short-acting medication with half-life of approximately two to three hours. This necessitated a dosing regimen of at least twice daily to achieve efficacy throughout the day. To provide a longer lasting single dose and ease the need for a mid-day dose, a formulation was developed that can be administered once a day. This extended-release drug product uses the proprietary SODAS™ (Spheroidal Oral Drug Absorption System) technology developed by Elan Corporation plc. A single dose of Focalin™ XR capsule is intended to release medication immediately after dosing followed by a second release approximately four hours after dosing.

The proposed product, Focalin™ extended release capsules, manufactured by Elan Holdings, Inc., is to be marketed as an oral dosage form in strengths of 5 mg, 10 mg, 20 mg [redacted]
Each capsule contains 5 mg, 10 mg, 20 mg [redacted] of dexmethylphenidate hydrochloride. The commercial manufacturing process for dexmethylphenidate hydrochloride extended release capsules

[redacted]



Adequate information was provided for the manufacturing of the drug product. In-process tests for IR and DR beads included Description, Identification, Assay, Related substances, Dissolution, and LOD. In-process test results of the IR and DR beads were provided by the applicant. On the basis of stability data of IR and DR beads stored for the [redacted] at long term storage conditions supports a holding-time of [redacted] the in-process components. The specifications for capsules included Description, Identification (HPLC and UV), Assay (HPLC), Related Substances (HPLC), Drug release (HPLC), Content Uniformity (HPLC), Enantiomer (chiral HPLC), and Residual solvents (GC). The batch analysis was provided for two batches of each strength of Dexmethylphenidate hydrochloride extended release capsules. The release and stability specifications for the drug product are identical except the additional specification for the [redacted]) and total impurities in stability specifications. Validated analytical methods were provided in the submission.

[redacted] batches of drug product [redacted] registration batches of each, 5 mg and 10 mg strengths, [redacted] registration batches of each, 20 [redacted] mg strength) were manufactured at the commercial manufacturing site, Elan Holdings, Inc., Gainesville, GA at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches. A typical drug product batch size consists of approximately [redacted] units of the 5 mg capsule strength, [redacted] of the 10 mg capsule, [redacted] of the 20 mg capsule, [redacted] respectively. It is indicated by the applicant that the actual batch size may vary minimally based upon the assay results and calculated fill weight for each IR and DR bead batches. Focalin™ extended release capsules will be marketed only into bottles with 38 mm child resistant caps. The bottle sizes [redacted]

The initial registration stability protocol was submitted to FDA for review and comment on 02-May-2003 (IND 63,885, Serial No. 004). The final protocol reflecting the agreed upon changes was submitted on 23-SEP-03 (approved on 01-OCT-03) with the agreement of adding full testing for 1 (one) batch of the 10 mg strength at initial and [redacted] month time point as a compatibility test for caramel capsule shell color to the original protocol submitted in N-004 on 02-MAY-03. The

The drug substance, dexmethylphenidate hydrochloride, is manufactured and supplied to the applicant by [redacted] according to the process and controls described in their DMF #s [redacted] Letters of Authorization to access these DMFs were provided for cross-reference. The DMF #s [redacted] were reviewed and found adequate by Drs. Chhagan Tele (01-MAR-05) and Huijeong Hahm (01-MAY-03), respectively. Dexmethylphenidate hydrochloride is a white to off-white, crystalline powder with two chiral centers. All the batches of dexmethylphenidate hydrochloride drug substance presented in the original NDA were manufactured at the [redacted] plant. Batch analysis data of three batches of drug substance used in manufacturing of drug product were provided. Validated analytical methods were provided in the DMF. A retest date of [redacted] has been established for the bulk dexmethylphenidate hydrochloride drug substance by [redacted] on the basis of [redacted] real time stability data for 3 commercial batches.

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

Focalin™ (dexmethylphenidate hydrochloride) extended release capsules will be marketed only into bottles. The bottle sizes [redacted] for 5 mg, 10 mg, and 20 mg capsules [redacted] The maximum recommended total daily dose is [redacted] /day. Novartis initially provided [redacted] of stability data at 25° C/60% RH and [redacted] stability data at 40° C/75% RH for registration batches of each strength, 5 mg, 10 mg, 20 mg [redacted] dexmethylphenidate hydrochloride extended release capsules. In amendment N-000(BC) dated 30-NOV-04, 12 months stability data at long term for registration batches of each strength, 5 mg, 10 mg, 20 mg [redacted] was provided. The applicant has requested a [redacted] expiration period (shelf life) for all strengths packaged in bottles.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Dispense in tight container (USP).

The applicant makes the usual post-approval stability commitments with regards to stability studies indicating that the first three production batches for each strength and each container/closure system will continue according to the approved stability protocols through the expiration dating period.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).

The Office of Compliance has found all manufacturing, testing, and packaging sites for drug substance and drug product acceptable.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-802 for Focalin™ extended release capsules is recommended to be granted **Approval** status from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.
Chemistry Team Leader Name: Thomas F. Oliver, Ph.D.
Project Manager Name: Richardae Taylor, Pharm.D.

C. CC Block

See DFS.

163 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Chhagan Tele
4/15/05 11:02:46 AM
CHEMIST

Thomas Oliver
4/15/05 11:08:43 AM
CHEMIST