CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-514

CHEMISTRY REVIEW(S)

NDA 21-514

Methypatch
(Methylphenidate Transdermal System)

Noven Pharmaceuticals, Inc

Sherita D. McLamore, Ph.D.
Division of Psychiatry Products
HFD-130

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-514

2. REVIEW # 2

3. REVIEW DATE: 12/14/05

4. REVIEWER: Sherita McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	7/25/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to NA	6/28/05

7. NAME & ADDRESS OF APPLICANT:

Name:	Noven Pharmaceuticals, Inc.
Address:	11960 SW 144th Street Miami, Florida
Representative:	David Lucking
Telephone:	305.964.3109

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MethyPatch®
b) Non-Proprietary Name / USAN: Methylphenidate Transdermal System
c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2, 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Attention Deficit Hyperactivity Disorder

11. DOSAGE FORM: Transdermal

12. STRENGTH/POTENCY: 1.10, 1.78, 2.21 and 2.97 mg/hour

13. ROUTE OF ADMINISTRATION: Percutaneous

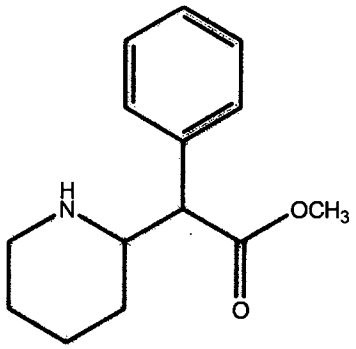
14. Rx/OTC DISPENSED: __X__Rx ___OTC

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:

Chemical Name: Methyl-alpha-phenyl-2-piperidineacetate
Molecular Formula: $C_{14}H_{19}NO_2$
Molecular Weight: 233.31



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF [redacted]	Type II	[redacted]	Manufacture of Methylphenidate Base	1	Adequate	04-25-03	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	10-10-02	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	4	N/A	N/A	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	3-16-02	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	4	N/A	N/A	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	09-16-02	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	11-12-02	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	7-22-97	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	3-27-03	N/A
DMF [redacted]	Type III	[redacted]	[redacted]	1	Adequate	01-10-01	N/A

[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
IND	54,732	Commercial IND Indication: Treatment of Attention Deficit Hyperactive Disorder (ADHD) Sponsor: Noven Pharmaceuticals

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	7/25/05	Office of Compliance
Pharm/Tox	Pending	N/A	Edward Fisher Ph.D.
Biopharm	Acceptable	3/31/03	Ronald Kavanagh, Ph.D.
Methods Validation	Pending		Sherita McLamore, Ph.D.
DMETS	Acceptable	N/A 10/23/02	Denise Toyer, R.Ph.
EA	Categorical Exclusion Granted	4-15-03	Sherita McLamore, Ph.D.

The Chemistry Review for NDA 21-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-514 should be approved.

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

N/A

II. Summary of Chemistry Assessments

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

Methylphenidate was originally investigated under IND 54,732 in 1997. It is a Class II compound and is a mild central nervous system stimulant. Methylphenidate is indicated for the treatment of patients with attention deficit hyperactive disorder (ADHD). Although this drug substance is the free base of the USP compound methylphenidate hydrochloride, it has not been approved for use as the drug substance in any product in the US.

The applicant included very limited information on the drug substance in this application. The drug substance is described as a white to off-white solid with a relatively low melting point (42.1°C). The molecular formula for the drug substance is $C_{14}H_{19}NO_2$ and the molecular weight is 233.31. The applicant indicates that the drug substance will be manufactured by [redacted] and references DMF [redacted] for the manufacture and controls of the drug substance. A letter of authorization is provided on page 38 of volume 3.

There is no information pertaining to the synthesis of the drug substance outlined in the NDA.

The drug product, Methyphenidate Transdermal System (MTS) is a three component drug-in-adhesive matrix. The system is made of acrylic pressure sensitive adhesive, silicone pressure sensitive adhesive and Methylphenidate. The applicant indicates that the drug product is available in four dosages and will be manufactured at the Noven Pharmaceuticals facility in Miami, Florida. The 27.5 mg patch is a 12.5 cm^2 rounded square that is 1 ½ X 1 ½ inches. The 41.3 mg patch is a 18.75 cm^2 rounded rectangle that is 1 ½ X 2 inches. The 55.0 mg patch is a 25 cm^2 rounded rectangle that is 1 ½ X 2 ½ inches. The — mg patch is a 37.5 cm^2 rounded rectangle that is 1 ½ X 3 7/8 inches. Each Methylphenidate Transdermal System will be — and individually packaged in a —-sealed —. The individually pouched units will be packaged into polyester trays containing the desired number (either — 30 units) with a — and sealed with —

The applicant proposed the proprietary name MethyPatch® for the drug product. The Office of Post–Marketing Drug Risk Assessment (OPDRA) has not posed any objections to the use of this name.

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

The Methylphenidate Transdermal System (MethyPatch®) is being developed for the treatment attention deficit hyperactive disorder. It is a once a day adhesive based — that provides a continuous delivery of the methylphenidate at a rate of release of — mg/hr per cm^2. The normal dose is delivered over — ours. The patches will be available in 12.5 mg/27.5 cm^2, 41.3 mg/18.75 cm^2, 55.0 mg/ 25 cm^2, and 82.5 mg/ 37.5 cm^2. The applicant also indicates that a —may be introduced at a later time if there is a need.

The applicant has requested a 26 month expiry for all potencies of the MethyPatch® systems. The 26 month expiry includes a 24 month shelf life and a 2 month in-use period. The applicant provided bracketed stability protocol. This bracketing design utilized the lowest (13.8 mg/6.25 cm^2), highest (110 mg/50cm^2) and one intermediate strength patch (41.3 mg/18.75 cm^2). Three batches of each of these potencies were placed on stability and stored in the intended commercial packaging —and 30 count trays). The applicant also submitted supporting stability data, however, the applicant has not provided adequate data to support a 26 month shelf life. The applicant was asked to submit a stability update for the drug product. The applicant included 24 month of long term stability data with 2 months in-use. The data included was acceptable and within the prescribed specification limits. The applicant has provided adequate data to support a **26-month expiry** (24-month shelf life with an additional 2-month in use period).

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-514 should be Approved from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
SMcLamore/Date
TOliver (TL)/Date
A (PM)/Date

C. CC Block
Orig. NDA 21-514
HFD-120/Division File
HFD-120/RTaylor
HFD-120/SMcLamore
HFD-120/TOliver

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Sherita McLamore
12/19/2005 09:34:52 AM
CHEMIST

Thomas Oliver
12/19/2005 10:26:09 AM
CHEMIST

NDA 21-514

Methypatch
(Methylphenidate Transdermal System)

Noven Pharmaceuticals, Inc

Sherita D. McLamore, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-514

2. REVIEW # 1

3. REVIEW DATE: 3/1/03

4. REVIEWER: Sherita McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	7/25/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Noven Pharmaceuticals, Inc.
Address:	11960 SW 144th Street Miami, Florida
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a) Proprietary Name: MethyPatch®

b) Non-Proprietary Name / USAN: Methylphenidate Transdermal System
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2, 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Attention Deficit Disorder

11. DOSAGE FORM: Transdermal

12. STRENGTH/POTENCY: 0.9, 1.35, 1.8 and 2.7mg/hour

13. ROUTE OF ADMINISTRATION: Percutaneous

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____**SPOTS product – Form Completed**

__X___Not a SPOTS product

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

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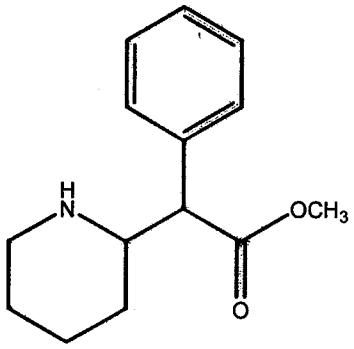

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DMF —	Type III	—	—	4	N/A	N/A	N/A
DMF —	Type III	—	—	1	Adequate	3-16-02	N/A
DMF —	Type III	—	—	4	N/A	N/A	N/A
DMF —	Type III	—	—	1	Adequate	09-16-02	N/A
DMF —	Type III	—	—	1	Adequate	11-12-02	N/A
DMF —	Type III	—	—	1	Adequate	7-22-97	N/A
DMF —	Type III	—	—	1	Inadequate	3-27-03	N/A
DMF —	Type III	—	—	1	Adequate	01-10-01	N/A

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The Chemistry Review for NDA 21-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-514 is approvable. The applicant will been sent a list of deficiencies and comments.

Methods validation will be submitted after all CMC deficiencies have been addressed.

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

N/A

II. Summary of Chemistry Assessments

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

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The applicant proposed the proprietary name MethyPatch® for the drug product. The Office of **Post–Marketing Drug Risk Assessment (OPDRA) has not posed any objections to the use of** this name.

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The applicant has requested a 26 month shelf life for all potencies of the MethyPatch® systems in the [redacted] and 30 count trays (V 4, page 543). As indicated in the stability section of this review, the applicant provided bracketed stability protocol. This bracketing design utilized the lowest (13.8 mg/6.25 cm^2), highest (110 mg/50cm^2) and one intermediate strength patch (41.3 mg/18.75 cm^2). Three batches of each of these potencies were placed on stability and stored in the intended commercial packaging ([redacted] and 30 count trays). The applicant also submitted supporting stability data, however, the applicant has not provided adequate data to support a 26 month shelf life. The applicant will be asked to submit a stability update for the drug product.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-514 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and

controls concerns related to the drug substance and the drug product as outlined in this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
A (PM)/Date

C. CC Block

Orig. NDA 21-514
HFD-120/Division File
HFD-120/AHomanny
HFD-120/SMcLamore
HFD-120/TOliver

44 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Sherita McLamore
4/15/03 02:33:58 PM
CHEMIST

Thomas Oliver
4/15/03 03:14:40 PM
CHEMIST