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APPLICATION NUMBER:

203752Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	203752 SS# 0000
Supporting document/s:	e-submission
Applicant's letter date:	12/29/2011
CDER stamp date:	12/29/2011
Product:	Proposed Proprietary name as (b) (4) (Estradiol transdermal system).was considered unacceptable by Division of Medication Error Prevention & Analysis.
Indication:	For treatment of moderate to severe vasomotor symptoms associated with menopause
Applicant:	Noven Pharmaceuticals, Inc, New York, NY
Review Division:	Reproductive & Urologic Products
Reviewer:	Krishan L. Raheja, D. V. M. Ph.D.
Supervisor/Team Leader:	Alex Jordan, Ph.D.
Division Director:	Audrey Gassman, M.D.
Project Manager:	George Lyght, RPh.
Date entered in Darrts	*5/9/2012:*

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203752 are owned by Noven Pharmaceuticals Inc. or are data for which Noven Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 203752 that Noven Pharmaceuticals Inc. 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203752.

1 Executive Summary

1.1 Introduction: The (b) (4) NDA is a 505b(1) application with a right of cross-reference to Novartis's Vivelle and Vivelle-Dot NDA 20-323 and NDA 20-538, respectively. (b) (4) is a multipolymeric adhesive, estradiol transdermal system (ETS) that releases 17β-estradiol continuously upon application to intact skin. (b) (4)

17β-estradiol is the primary estrogenic hormone secreted by the human ovary. Loss of ovarian estrrdiol secretion at the onset of menopause or after bilateral oophorectomy is associated with vasomotor symptoms as hot flashes and night sweats. Systemic hormone therapy is considered as standard therapeutic option for the treatment of hot flashes. Treatment of moderate to severe menopausal symptoms is the primary indication for systemic hormone therapy.

The proposed indication for (b) (4) is for the treatment of moderate to severe vasomotor symptoms associated with menopause. Data to support the use of (b) (4) for the proposed indication comes from previous conducted clinical trials with Vivelle.

1.2 Brief Discussion of Nonclinical Findings: Based on discussion with the sponsor in a preIND meeting on 9/11/07, it was agreed that no additional preclinical studies for (b) (4) were necessary to support its marketing registration because:

1. (b) (4) .

2. Preclinical studies have shown that Vivelle-Dot is neither a primary skin irritant nor a dermal sensitizer.

3. The nonclinical pharmacology, pharmacokinetics, and toxicology of 17β-estradiol delivered via an estradiol transdermal system are well characterized as summarized in the current Package Inserts for Vivelle and Vivelle-Dot.

As shown in table below, (b) (4) is available in (b) (4) strengths that have been designed to deliver the same dosage levels of estradiol as Vivelle-Dot, but from a smaller active surface area.

Vivelle, Vivelle-Dot and (b) (4) dosage forms:

Strength	Vivelle	Vivelle-Dot	(b) (4)
Active surface area/patch size			
0.025 mg/day	7.25 cm^2	2.5 cm^2	(b) (4)
0.0375 mg/day	11.0 cm^2	3.75 cm^2	2.48 cm
0.05 mg/day	14.5 cm^2	5.0 cm^2	3.30 cm^2
0.075 mg/day	22 cm^2	7.5 cm^2	4.95 cm^2
0.1 mg/day	29cm^2	10 cm^2	6.60 cm^2
Estradiol content/unit			
0.025 mg/day	2.17 mg	0.39 mg	(b) (4)
0.0375 mg/day	3.28 mg	0.585 mg	0.62 mg
0.05 mg/day	4.33 mg	0.78 mg	0.83 mg
0.075 mg/day	6.57 mg	1.17 mg	1.24 mg
0.1 mg/day	8.66 mg	1.56 mg	1.65 mg

Note: Vivelle-Dot was approved under NDA 20-538 on 7/31/1996.based on bioequivalent to Vivelle. Vivelle was approved under NDA 20-323 on 10/28/1994.

1.3 Recommendations

1.3.1 Approvability: Based on the results of the preclinical studies demonstrating lack of skin irritation in rabbit and delayed sensitization in guinea pig and patch safety in clinical trials, Pharmacology/Toxicology will recommend approved of NDA 203752 for (b) (4) for treatment of moderate to severe vasomotor symptoms associated with menopause.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Sponsor has provided Draft Labeling Text

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/s/

KRISHAN L RAHEJA
05/09/2012

ALEXANDER W JORDAN
05/09/2012

45 Day NDA Meeting Checklist
Pharmacology/Toxicology

NDA Number: 203752 **Date:** 2-13-2012
Drug Name: [redacted] (b) (4) **(estradiol transdermal system)** **Reviewer:** Krishan L. Raheja
Sponsor: Noven Pharmaceuticals Inc.

Date CDER Received: 12-29-2011
Filing Date: 2-27-2012
User Fee Date:
Expected Date of Draft Review: -

On initial overview of the Pharm/Tox portion of the NDA application

	ITEM	YES / NO	COMMENTS
1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?		In a pre-IND meeting on 9-11-2007 it was agreed that no additional preclinical studies for [redacted] (b) (4) were necessary to support its marketing registration because: 1. [redacted] (b) (4) 2. Preclinical studies have shown that Vivelle-Dot is neither a primary skin irritant nor a dermal sensitizer. 3. The nonclinical pharmacology, pharmacokinetics, and toxicology of 17β-estradiol delivered via an estradiol transdermal system are well characterized and are summarized in the current Package Inserts for Vivelle and Vivelle-Dot.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?		NA
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?		NA
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?		NA

5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?		NA
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	YES	
7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?		NA
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?		NA
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	NO	
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	
11)	Reasons for refusal to file:		

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/s/

KRISHAN L RAHEJA
02/13/2012

ALEXANDER W JORDAN
02/13/2012