

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204516Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**Division of Reproductive and Urologic Products  
Center for Drug Evaluation and Research**

**Date:** 5/10/2013

**Reviewer:** Alex Jordan, Ph.D.  
Expert Reviewer

**NDA #/SS#/date:** 204516

**Sponsor:** Noven Pharmaceuticals

**Drug Product:** Paroxetine mesylate

**Indication:** Vasomotor symptoms in post-menopausal women

**Recommended Action:** Approval

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**Background:**

**Pharmacology:** Paroxetine is approved for the treatment of psychiatric conditions including major depressive, obsessive compulsive, panic, and generalized anxiety disorders. There were no nonclinical safety concerns identified for use of paroxetine for the new indication of treatment of vasomotor symptoms in postmenopausal women. The proposed dose for treatment of vasomotor symptoms of 7.5 mg is lower than that approved for other indications and requires no additional toxicological evaluation.

**Outstanding nonclinical issues:** None

**Conclusion:** I concur with the primary nonclinical reviewer, Dr. McKinney, in recommending an approval action for this NDA.

CDTL Review:

## 4. Nonclinical Pharmacology/Toxicology

*The topics below should be addressed by the CDTL. The CDTL should re-iterate, emphasize or expand upon any issue from the Pharmacology/Toxicology review and from discussions with the Pharm/Tox review team as deemed appropriate. Particular attention should be paid to any potential clinical safety concern emanating from nonclinical studies, including but not limited to results of acute or chronic toxicity studies, genotoxicity or carcinogenicity studies, or reproductive toxicology studies.*

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).
- Carcinogenicity
- Reproductive toxicology
- Other notable issues (resolved or outstanding)

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/s/  
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ALEXANDER W JORDAN  
05/14/2013

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number:	204516
Supporting document/s:	NDA 20-031 (Paxil®) NDA 21-299 (Pexeva®) and IND 76636
Applicant's letter date:	28 Aug 2012
CDER stamp date:	28 Aug 2012
Product:	Paroxetine mesylate
Indication:	Vasomotor symptoms in post-menopausal women
Applicant:	Noven Pharmaceuticals
Review Division:	Division of Reproductive and Urologic Drugs
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Alex Jordan, PhD
Division Director:	Hylton Joffe, MD
Project Manager:	Kimberly Shiley, RN

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204516 are owned by Noven Pharmaceuticals or are data for which Noven has obtained a written right of reference. Any information or data necessary for approval of 204516 that Noven Pharmaceuticals 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Noven Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of 204516.

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# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

This is a 505(b)2 application. Noven Pharmaceuticals is relying on previous findings of safety for the active ingredient paroxetine from NDA 20-031 (Paxil®) and is cross-referencing its own NDA 21-299 and IND 76636 for paroxetine mesylate (Pexeva®) for support of this NDA.

There were no nonclinical safety concerns identified for use of paroxetine for the new indication of vasomotor symptoms (VMS) in postmenopausal women. Based on previous approval of paroxetine at a dose greater than the proposed dose for treatment of VMS (7.5 mg/day), PharmTox finds NDA 204516 approvable.

### 1.1.2 Additional Non Clinical Recommendations

None

### 1.1.3 Labeling

The relevant nonclinical sections of the sponsor's proposed labeling are shown below with suggested edits. Edits were made to bring text into concordance with the recommended PLR format. Suggested deletions are shown as strikethroughs, and suggested additions are highlighted in yellow.

It should be noted that current labels for paroxetine drug products (Paxil®, Pexeva®) do not contain the pharmacological class in the **INDICATIONS AND USAGE** section. Paroxetine has a designated established pharmacological class (EPC) of 'serotonin reuptake inhibitor', with recommended text for the label of 'selective serotonin reuptake inhibitor (SSRI).

(b) (4)

#### Animal

(b) (4)

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are

(b) (4)

approximately 65 (rat) and 16 (rabbit) the MRHD for VMS on a mg/m basis.

(b) (4)

no (b) (4) teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately

(b) (4)

the MRHD for VMS on a mg/m basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Nonclinical studies have shown that paroxetine (b) (4) is a (b) (4) (SSRI). (b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis/ Mutagenesis and Impairment of Fertility

#### Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses (b) (4)

were approximately 16 (mouse) and 26 (rat) times the MHRD for VMS. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

#### Mutagenesis

~~Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.~~

(b) (4)

#### Impairment of Fertility

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 19 times the MRHD for VMS on a mg/m<sup>2</sup> basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (65 times and 32 times the MHRD for VMS on a mg/m<sup>2</sup> basis, respectively).

### 1.2 Brief Discussion of Nonclinical Findings

There were no new nonclinical studies submitted to support this NDA. Nonclinical findings relevant to the clinical use of paroxetine mesylate for VMS are adequately captured in labeling.



## 2 Drug Information

### 2.1 Drug

#### 2.1.1 CAS Registry Number

217797-14-3

#### 2.1.2 Generic Name

Paroxetine mesylate

#### 2.1.3 Code Name

none

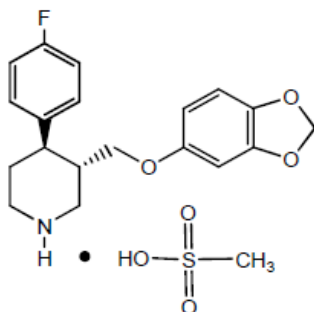
#### 2.1.4 Chemical Name

(-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy)methyl] piperidine, mesylate

#### 2.1.5 Molecular Formula/Molecular Weight

C<sub>19</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub>•CH<sub>3</sub>SO<sub>3</sub>H / 425.46

#### 2.1.6 Structure



#### 2.1.7 Pharmacologic class

Established pharmacological class: serotonin reuptake inhibitor

### 2.2 Relevant IND/s, NDA/s, and DMF/s

IND 76636	paroxetine mesylate
NDA 21-299: PEXEVA®	paroxetine mesylate
NDA 20-031: PAXIL®	paroxetine hydrochloride
DMFs	(b) (4)

## 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

Table 2.3.P.1-1. Composition of Paroxetine mesylate capsules, 7.5 mg

Component	Reference std	Function	mg/capsule	%w/w
Paroxetine mesylate	In house (NDA 21-299)	Drug substance	9.69*	(b) (4)
Dibasic calcium phosphate (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)
Sodium starch glycolate	NF			
Magnesium stearate	NF			
Capsule Shell	Manufacturer			--
Total			214.0	100.0

\*equivalent to 7.5 mg paroxetine base

### 2.3.2 Comments on Novel Excipients

None

### 2.3.3 Comments on Impurities/Degradants of Concern

None

## 2.4 Proposed Clinical Population and Dosing Regimen

Intended clinical population: postmenopausal women experiencing moderate to severe vasomotor symptoms (hot flashes). Proposed dose: 7.5 mg/day.

## 2.5 Regulatory Background

Paroxetine hydrochloride (PAXIL®; approved in 1992) and paroxetine mesylate (PEXEVA®; approved in 2003) are indicated for treatment of psychiatric conditions including major depressive, obsessive compulsive, panic, and generalized anxiety disorders. They are currently marketed in 10, 20, 30, and 40 mg oral tablet dose forms.

Development of paroxetine mesylate for treatment of VMS was begun in 2007 under IND 76636. At that time, DRUP indicated that no new nonclinical studies would be requested. At the pre-NDA meeting in 2012, DRUP concurred with the sponsor that only a high level summary in the form of a Nonclinical Overview would be sufficient to file the NDA.

# 11 Integrated Summary and Safety Evaluation

There were no nonclinical safety concerns identified for use of paroxetine for the new indication of treatment vasomotor symptoms (VMS) in postmenopausal women. Approved indications for paroxetine mesylate allow dosing up to 60 mg/day. The proposed dose for treatment of vasomotor symptoms of 7.5 mg is lower than that approved for other indications and therefore required no additional toxicological evaluation.

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/s/  
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LESLIE C MCKINNEY  
02/01/2013

ALEXANDER W JORDAN  
02/04/2013