

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204516Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Hylton V. Joffe, M.D., M.M.Sc.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	204516
<b>Applicant Name</b>	Noven Therapeutics, LLC
<b>Date of Submission</b>	August 28, 2012
<b>PDUFA Goal Date</b>	June 28, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Brisdelle (paroxetine)
<b>Dosage Forms / Strength</b>	7.5 mg capsules
<b>Proposed Indication(s)</b>	For the treatment of moderate to severe vasomotor symptoms associated with menopause
<b>Action</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Ronald Orleans, M.D.
Statistical Review	Jia Guo, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Leslie McKinney, Ph.D. and Alex Jordan, Ph.D.
CMC Review	Caroline Strasinger, Ph.D. and Moo-Jhong Rhee, Ph.D.
Biopharmaceutics Review	Deepika Arora Lakhani, Ph.D. and Sandra Suarez Sharp, Ph.D.
Clinical Pharmacology Reviews	Li Li, Ph.D. and Myong-Jin Kim, Pharm.D.
OSI	Roy Blay, Ph.D., Janice Pohlman, M.D., M.P.H. and Susan Thompson, M.D.
CDTL Review	Lisa Soule, M.D.
OSE/DMEPA	Manizheh Siahpoushan, Pharm.D. and James Schlick, RPh, MBA
OMPI/DMPP	Twanda Scales, R.N., M.S.N./Ed., Melissa Hulett, R.N., B.S.N., M.S.B.A. and LaShawn Griffiths, R.N., M.S.H.S.-P.H., B.S.N.
OHOP/DOP1 Consultation	Laleh Amiri-Kordestani, M.D. and Patricia Cortazar, M.D.
DPP Consultation	Lucas Kempf, M.D., Robert Levin, M.D. and Mitchell Mathis, M.D.
OPDP	Lynn Panholzer, Pharm.D.
SEALD	Abimbola Adebawale, Ph.D. and Eric Brodsky, M.D.
Pediatric and Maternal Health Staff	Jeanine Best, M.S.N., R.N., P.N.P. and Lynne Yao, M.D.

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

CMC=Chemistry, Manufacturing, Controls

DMEPA=Division of Medication Error Prevention and Analysis

DMPP=Division of Medical Policy Programs

DPP=Division of Psychiatric Products

DPV=Division of Pharmacovigilance

OMPI=Office of Medical Policy Initiatives

OHOP/DOP1=Office of Hematology Oncology Products/Division of Oncology Products 1

OPDP=Office of Prescription Drug Promotion

OSE=Office of Surveillance and Epidemiology

OSI=Office of Scientific Investigations

SEALD=Study Endpoints and Labeling Development

## Signatory Authority Review

### 1. Introduction

Noven Therapeutics, LLC has submitted this 505(b)(2) new drug application (NDA) for paroxetine mesylate (tradename Brisdelle), seeking an indication for the treatment of moderate to severe vasomotor symptoms (hot flushes) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor. The mechanism by which paroxetine may reduce hot flushes is unknown. If this NDA is approved, paroxetine would be the first and only FDA-approved non-hormonal treatment for this condition.

Paroxetine is the active ingredient in Paxil (paroxetine hydrochloride) and Pexeva (paroxetine mesylate), which are approved treatments for several psychiatric conditions, including major depressive disorder, obsessive-compulsive disorder, panic disorder and generalized anxiety disorder. Both products are available as 10, 20, 30 and 40 mg tablets and are usually dosed in the morning, starting at 10-20 mg and titrating to a maximum recommended dose of 40-60 mg, depending upon the indication. The Applicant is proposing a 7.5 mg dose for Brisdelle given once daily at bedtime for the treatment of moderate to severe vasomotor symptoms. The Applicant is abbreviating the Brisdelle development program by relying upon data from its own Pexeva NDA and by also relying on FDA's findings of safety for Paxil (for which it does not have right of reference).

This document serves as the decisional memorandum for the application.

### 2. Background

Hot flushes due to menopause usually begin as a sensation of heat on the upper body that becomes generalized, lasting a few minutes. The cause of hot flushes is unknown but is thought to be related to thermoregulatory dysfunction. Hot flushes occur in about 75% of menopausal women in the United States. Most of these women have symptoms for more than one year and, if untreated, symptoms usually spontaneously resolve within a few years of onset. Women with mild symptoms (sensation of heat without sweating) do not usually require pharmacologic therapy. Estrogen (for women without a uterus) and estrogen/progestin combination products (for those with a uterus) are the only FDA-approved treatments for hot flushes. These products are indicated for the treatment of moderate (sensation of heat with sweating but able to continue activity) to severe vasomotor symptoms (sensation of heat with sweating causing cessation of activity).

Although hormonal treatment is highly effective, these products are contraindicated in women who have breast cancer (or a history of breast cancer), venous thromboembolism (or a history of venous thromboembolism) or thrombophilia, and in those with a history of stroke or myocardial infarction. Based on the Women's Health Initiative, risks of estrogen/progestin

hormonal therapy include coronary artery disease, stroke, venous thromboembolism and breast cancer. Risks for estrogen alone therapy include stroke and venous thromboembolism, but do not appear to include coronary artery disease or breast cancer. Subsequent analyses of the data from the Women's Health Initiative appear to show that absolute risks are considerably lower in younger age women (those 50-59 years old), which is the patient population most likely to require pharmacologic therapy for hot flashes.

Currently, women who seek treatment for vasomotor symptoms but cannot or will not use hormonal therapy may try off-label use of gabapentin, selective serotonin reuptake inhibitors, including paroxetine, or selective norepinephrine reuptake inhibitors. Some women also try soy products, herbal therapies (black cohosh) or alternative therapies such as acupuncture. However, the effectiveness and safety of these products and therapies have not been established.

Clearly, there is an unmet need for an FDA-approved non-hormonal treatment option for vasomotor symptoms. These symptoms can be very bothersome and can cause discomfort, embarrassment and disruption of sleep. However, when considering an analysis of risk/benefit of potential new therapies it is important to consider that vasomotor symptoms are not life-threatening.

### 3. CMC

The drug product is an immediate-release capsule that contains 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base). The drug substance used to manufacture Brisdelle is the same as that used to manufacture Pexeva. (b) (4) all excipients are within acceptable levels. The Chemistry/Manufacturing/Controls (CMC) reviewers have found the minor differences between Brisdelle and Pexeva (e.g., capsule for Brisdelle vs. tablet for Pexeva (b) (4) to be acceptable. The CMC reviewers and the Applicant have agreed to a 36-month expiration dating period. In addition, the CMC reviewers agree with the Applicant's request for a categorical exclusion from environmental assessment. The Applicant originally proposed to manufacture the drug product at two sites (Norwich Pharmaceuticals in North Norwich, NY and (b) (4)). However, the Applicant withdrew the (b) (4) site from the NDA after FDA inspectors identified incomplete or unsuccessful methods validation at that site that would have precluded approval of the NDA. The Applicant has committed to performing stability studies on the first three commercial batches of drug product. A minimum of one lot per year in each packaging configuration ((b) (4) blister packs) will be placed on long-term stability and tested accordingly.

The to-be-marketed formulation is identical to the formulation tested in the Phase 3 program.

The Office of Compliance issued an acceptable recommendation after the Applicant withdrew the (b) (4) drug product manufacturing site from the NDA. All other outstanding CMC issues, including labeling, have been adequately addressed. Therefore, CMC

recommends approval of the NDA. See the reviews by Caroline Strasinger, Ph.D. for further details.

## **4. Nonclinical Pharmacology/Toxicology**

The Nonclinical Pharmacology/Toxicology reviewers recommend approval of the NDA, noting that paroxetine is already approved at doses higher than the 7.5 mg dose proposed for the treatment of moderate to severe vasomotor symptoms. No new nonclinical studies were requested or conducted under the Brisdelle NDA.

The nonclinical pharmacology/toxicology program is abbreviated by relying upon FDA's findings from the Pexeva and Paxil NDAs.

See the reviews by Leslie McKinney, Ph.D. and Alexander Jordan, Ph.D. for details.

## **5. Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology reviewers find the NDA acceptable. Most of the clinical pharmacology data in support of the NDA have been previously reviewed for the Paxil and Pexeva NDAs. Key findings are summarized below. See the review by Li Li, Ph.D. for details.

The Brisdelle NDA contains one clinical pharmacology study (N30-005), which evaluated the pharmacokinetic profile of paroxetine after single and repeated dosing of paroxetine 7.5 mg in postmenopausal women. This study showed a T<sub>max</sub> for paroxetine of about 6 hours, a mean elimination half-life of about 17 hours and a 10-fold accumulation index. The pharmacokinetic parameters of paroxetine were highly variable, which is consistent with findings from the Paxil and Pexeva clinical pharmacology studies.

Selected pertinent findings from the Paxil and Pexeva NDAs include the following:

- The absorption of paroxetine is not affected by food
- Paroxetine undergoes extensive metabolism, in part due to CYP2D6. Saturation of this enzyme appears to account for non-linearity of paroxetine pharmacokinetics with increasing dose and increasing duration of treatment. In addition, paroxetine causes irreversible auto-inhibition of CYP2D6. Therefore, concomitant use of paroxetine with other medications metabolized by CYP2D6 may necessitate a dose reduction of these other medications. The Applicant did not conduct any drug-drug interaction studies using the 7.5 mg paroxetine dose. The clinical pharmacology reviewers agree that all the drug-drug interactions in the Pexeva label can be extrapolated to the current product.
- Paroxetine's metabolites are considered inactive based on the extent to which they inhibit serotonin uptake.

- There is a two-fold increase in overall exposure to paroxetine in patients with hepatic impairment or moderate renal impairment and a four-fold increase in overall exposure in patients with severe renal impairment. Dosage adjustment is not needed for Brisdelle because the 7.5 mg dose is lower than the recommended 10 mg/day starting dose of Paxil and Pexeva for patients with hepatic or severe impairment.
- Elderly patients administered Paxil had minimum plasma concentrations of paroxetine that were about 70-80% higher than that seen in younger patients. Dosage adjustment is not needed for Brisdelle because the 7.5 mg dose is lower than the 10 mg/day starting dose of Paxil and Pexeva recommended for elderly patients.
- There is a potential interaction between paroxetine and the breast cancer treatment, tamoxifen. CYP2D6 is a key enzyme responsible for generating the active tamoxifen metabolite, endoxifen. Inhibition of CYP2D6 may lower plasma concentrations of endoxifen, and thereby reduce the effectiveness of tamoxifen. Both the Paxil and Pexeva labels contain the following Precaution: “Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine’s irreversible inhibition of CYP2D6 (see Drug Interactions). However, other studies have failed to demonstrate such a risk. It is uncertain whether the coadministration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. One study suggests that the risk may increase with longer duration of coadministration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.” After obtaining input from the Division of Oncology Products 1, we revised this language accordingly for Brisdelle, recommending that the healthcare provider weigh the likely benefit of Brisdelle versus the risk of possible decreased tamoxifen effectiveness and consider avoiding concomitant use of Brisdelle. See the consultation by Laleh Amiri-Kordestani, M.D. for details.

#### Biopharmaceutics:

The Biopharmaceutics reviewers and the Applicant have reached agreement on the *in vitro* dissolution method and dissolution acceptance criterion. In addition, the Biopharmaceutics reviewers agree that the Applicant has sufficiently bridged drug product manufactured at the Norwich Pharmaceuticals and (b) (4) sites based on dissolution profile comparisons. This latter determination is currently moot because the Applicant has subsequently withdrawn the (b) (4) manufacturing site from the NDA (see the CMC Section). See the reviews by Deepika Arora Lakhani, Ph.D. for further details.

## **6. Clinical Microbiology**

Not applicable.

## 7. Clinical/Statistical-Efficacy

This section focuses on the design and efficacy results for the two phase 3 clinical trials. For further details, see the Medical Officer review by Ronald Orleans, M.D., the Cross-Discipline Team Leader memorandum by Lisa Soule, M.D. and the statistical review by Jia Guo, Ph.D. All three reviewers have concluded that the totality of the evidence supports the efficacy of Brisdelle for the treatment of moderate to severe vasomotor symptoms associated with menopause and recommend approval of the NDA.

Phase 2 Study (N30-002): This randomized, double-blind, placebo-controlled exploratory study randomized 101 postmenopausal women with vasomotor symptoms to eight weeks of treatment with paroxetine 7.5 mg daily or placebo. Based on favorable findings, the Applicant chose to test only this dose in the Phase 3 program. The Applicant also considered the results from two published studies, one testing 10 mg and 20 mg of paroxetine vs. placebo and the other testing 12.5 mg and 25 mg of controlled-release paroxetine vs. placebo. The Applicant noted that in each of these published studies the efficacy with the lower tested dose appeared similar to the efficacy with the higher tested dose and that there were fewer reported adverse events with the lower doses. Based on these observations, the Applicant concluded that a dose of 7.5 mg might also show efficacy with an improved safety profile. Because the Applicant did not conduct a dose-ranging study and did not incorporate more than one dose into the Phase 3 program, it is not clear how the 7.5 mg dose compares to lower or higher doses with respect to efficacy and safety.

Overview of the Phase 3 Program: The Applicant conducted two, randomized, double-blind, placebo-controlled phase 3 clinical trials (N30-003 and N30-004) that enrolled postmenopausal women  $\geq 40$  years old with more than 7-8 moderate to severe hot flushes per day (or 50-60 per week). Both trials had a 12-day single-blind placebo run-in period then randomized those who continued to meet hot flush eligibility criteria to receive paroxetine 7.5 mg or placebo, taken once daily at bedtime. Study N30-003 had a 12-week treatment period. Study N30-004 had a 24-week treatment period.

Tamoxifen use was not permitted during the course of the trials. Patients with cancer or a history of cancer were otherwise not excluded. There were also no exclusion criteria related to venous thromboembolism, stroke or stable cardiac disease. However, it appears that the trials did not ultimately enroll many patients with these comorbidities. For example, Dr. Soule identified a total of only five patients with breast cancer who were randomized in the Phase 3 trials. Therefore, the enrolled population was not enriched with patients who were unable to take hormonal therapy.

Both phase 3 trials used the standard co-primary efficacy endpoints, as recommended in the draft Guidance for Industry entitled “Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation.” The recommendations in this draft guidance have been consistently used by sponsors of hormonal and non-hormonal products intended to treat vasomotor symptoms. These four co-primary efficacy endpoints are:

- Change in the frequency of moderate to severe hot flushes from baseline to Week 4
- Change in the frequency of moderate to severe hot flushes from baseline to Week 12
- Change in the severity of moderate to severe hot flushes from baseline to Week 4
- Change in the severity of moderate to severe hot flushes from baseline to Week 12

Severity of hot flushes was defined in the usual manner – mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity) or severe (sensation of heat with sweating causing cessation of activity).

The severity score at each timepoint (e.g., baseline, Week 4, Week 12) was calculated as follows:

$$\frac{(2 * \text{number of moderate hot flushes}) + (3 * \text{number of severe hot flushes})}{\text{Total number of moderate + severe hot flushes}}$$

As noted by Dr. Soule, severity scores calculated in this manner have shortcomings. For example, Dr. Soule discusses how a woman with 10 moderate and 10 severe hot flushes at baseline will have an unchanged severity score even if she has a decline to 1 moderate and 1 severe hot flush post-treatment. As another example, a woman with 10 moderate and 10 severe hot flushes at baseline who has 0 moderate and 5 severe hot flushes post-treatment will have a severity score that increases from 2.5 to 3.0. In both of these examples, one would have expected the severity score to decline.

The Division has more typically used a slightly different formula for calculating the post-baseline (e.g., Week 4 and Week 12) severity scores that includes the number of mild symptoms in both the numerator and denominator. However, this approach appears to have its own limitations. For example, a woman who at baseline has 10 mild hot flushes, 10 moderate hot flushes and 10 severe hot flushes will have a severity score of 2.5. If this woman still has 10 mild, 10 moderate and 10 severe hot flushes post-treatment, the severity score will decline to 2.0, when one would have expected the severity score to remain unchanged. As another example, a woman with 10 mild, 10 moderate and 10 severe hot flushes at baseline who has 1 mild, 1 moderate and 5 severe hot flushes post-treatment will have an increase in the severity score from 2.5 to 2.6 when one would have expected a reduction in the severity score.

These shortcomings should be considered when assessing the severity of vasomotor symptoms.

Important pre-specified secondary endpoints included an assessment of clinical meaningfulness for the reduction in hot flush frequency (Study N30-003) and an assessment for persistence of efficacy at Week 24 (Study N30-004).

Patient Demographics: In the Phase 3 trials, the mean age was about 55 years, most patients were Caucasian (65% in N30-003 and 76% in N30-004) or Black (33% in N30-003 and 22% in N30-004), and most patients had natural (~80%) rather than surgical menopause (~20%).

Primary Efficacy Endpoints: For both trials, the primary efficacy analysis was conducted on the modified-intent-to-treat population (randomized patients with valid baseline hot flush diary data who received  $\geq 1$  dose of randomized treatment and had  $\geq 1$  day of on-treatment diary data). The data were not normally distributed, therefore, the Applicant used the pre-specified alternate non-parametric analysis (rank-ANCOVA) instead of the repeated-measures analysis that would have been used had the data been normally distributed. The Applicant used last-observation-carried-forward to impute missing data as a sensitivity analysis.

Both treatment groups had a comparable completion rate in Study N30-003 (89% for paroxetine vs. 90% for placebo). Study N30-004 had a lower completion rate (83% with paroxetine and 77% with placebo) than Study N30-003, presumably due to the longer treatment duration of 24 weeks. The higher completion rate for paroxetine compared to placebo in Study N30-004 is mainly driven by discontinuations due to patient request (5% with paroxetine vs. 12% with placebo).

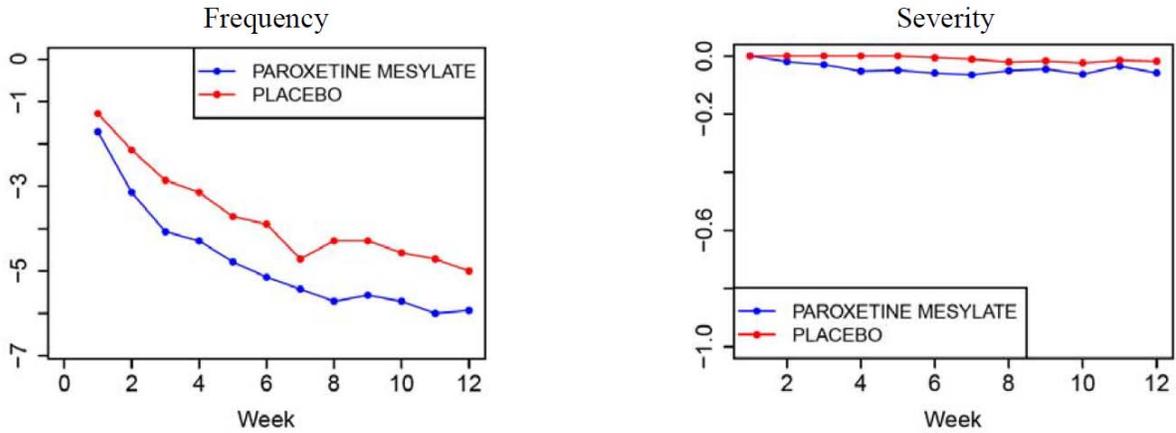
In both trials, the median number of moderate to severe hot flushes at baseline was about 10 per day. In both trials, paroxetine resulted in statistically significant reductions in the frequency of moderate to severe hot flushes relative to placebo at both Weeks 4 and 12 (Tables 1 and 2). The median treatment difference was -1.2 to -1.3 fewer moderate to severe hot flushes per day with paroxetine compared to placebo at Week 4 and -0.9 to -1.7 fewer moderate to severe hot flushes per day at Week 12. Changes over time are shown graphically in Figures 1 and 2.

In both trials, the median hot flush severity score at baseline was about 2.50. In both trials, the median reduction in severity score with paroxetine relative to placebo was about -0.05 at Weeks 4 and 12. This small treatment effect (about a 2% decline from baseline relative to placebo) was statistically significant at Week 4 in both trials and at Week 12 in Study N30-004 (Tables 1 and 2).

**Table 1. Study N30-003: Efficacy analyses based on moderate to severe hot flushes Modified intent-to-treat population (ITT) (Adapted from Table 5 in Dr. Guo’s review)**

	Frequency/Day		Severity	
	Paroxetine N=306	Placebo N=308	Paroxetine N=306	Placebo N=308
<b>Baseline</b>				
Median	10.4	10.4	2.54	2.54
<b>Week 4 (co-primary)</b>	n=289	n=293	n=281	n=289
Median change from baseline	-4.3	-3.1	-0.05	0.00
Median treatment difference	-1.2 (p<0.0001)		-0.05 (p<0.01)	
<b>Week 12 (co-primary)</b>	n=264	n=274	n=236	n=253
Median change from baseline	-5.9	-5.0	-0.06	-0.02
Median treatment difference	-0.9 (p<0.01)		-0.04 (p=0.17)	
p-values based on rank-ANCOVA model				

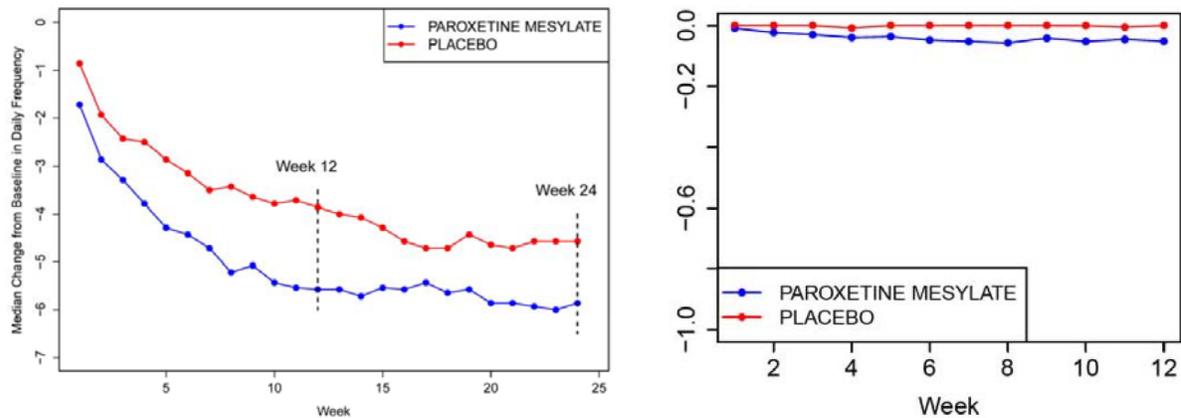
**Figure 1. Median changes in the frequency and severity of moderate to severe hot flashes in Study N30-003 (from Figure 1 in Dr. Guo’s review)**



**Table 2. Study N30-004: Efficacy analyses based on moderate to severe hot flashes Modified intent-to-treat population (Adapted from Table 6 in Dr. Guo’s review)**

	Frequency/Day		Severity	
	Paroxetine N=285	Placebo N=285	Paroxetine N=285	Placebo N=285
<b>Baseline</b>	n=284	n=284	n=284	n=284
Median	9.9	9.6	2.54	2.52
<b>Week 4 (co-primary)</b>	n=276	n=274	n=268	n=271
Median change from baseline	-3.8	-2.5	-0.04	-0.01
Median treatment difference	-1.3 (p<0.0001)		-0.03 (p=0.04)	
<b>Week 12 (co-primary)</b>	n=257	n=244	n=245	n=236
Median change from baseline	-5.6	-3.9	-0.05	0.00
Median treatment difference	-1.7 (p=0.0001)		-0.05 (p<0.01)	
p-values based on rank-ANCOVA model				

**Figure 2. Median changes in the frequency and severity of moderate to severe hot flashes in Study N30-004 (from Figures 2 and 5 in Dr. Guo’s review)**



Selected Secondary Efficacy Endpoints:

Clinical meaningfulness in Study N30-003: The Division has routinely requested an analysis of clinical meaningfulness when there is a statistically significant, but modest (treatment difference of less than two per day) reduction in the frequency of moderate to severe hot flashes relative to placebo at Weeks 4 and 12. Drs. Orleans, Soule, and Guo discuss in detail the Applicant’s pre-specified approach used to assess clinical meaningfulness. Briefly, all patients (including those on placebo) were asked at Weeks 4 and 12 to describe how their hot flashes compared to the hot flashes they were experiencing before starting study medication. Patients rated their response on a 7-point patient global impression scale ranging from (1) very much better to (7) very much worse. We focused on the analysis that classified patients as “satisfied” if they responded “very much better” or “much better”. Patients with other responses were classified as “unsatisfied”. Using these data, a receiver operating characteristic (ROC) curve was generated to determine the minimum reduction in the frequency of moderate to severe hot flashes that would translate into a clinically meaningful effect. As shown in Table 3, the calculated threshold was -4.0 at Week 4 and -5.3 at Week 12. Therefore, women were considered responders at Week 4 if the mean daily frequency of moderate to severe hot flashes was reduced more than 4.0/day from baseline at Week 4. Similarly, women were considered responders at Week 12 if the mean daily frequency of moderate to severe hot flashes was reduced more than -5.3/day from baseline at Week 12. Table 3 summarizes the percentages of responders in the paroxetine and placebo groups at Week 4 and 12, together with nominal p-values (the p-values were not controlled for type 1 error).

<b>Table 3. Clinical meaningfulness analysis: Percent responders in Study N30-003</b>				
<b>Modified intent-to-treat population</b>				
<b>(Adapted from Table 8 in Dr. Guo's review)</b>				
<b>Visit</b>	<b>Threshold</b>	<b>Paroxetine Responders n/N (%)</b>	<b>Placebo Responders n/N (%)</b>	<b>Nominal p-value</b>
Week 4	-4.0	152/301 (50%)	114/305 (37%)	0.001
Week 12	-5.3	153/301 (51%)	131/305 (43%)	0.055

Persistence of benefit at Week 24 in Study N30-004: For this pre-specified analysis, patients were considered responders if they achieved  $\geq 50\%$  reduction from baseline in the frequency of moderate to severe hot flushes at Week 24. Patients with a smaller reduction in hot flush frequency and those who prematurely discontinued from the trial were considered non-responders. Based on this analysis, the responder rate at Week 24 was 48% (135/284) for paroxetine and 36% (103/284) for placebo (nominal p-value  $< 0.01$ ). These data show that the treatment benefit for paroxetine is maintained through 24 weeks (the latest timepoint assessed). This finding is clinically important for patients who may choose to use Brisdelle because vasomotor symptoms associated with menopause tend to be chronic.

## 8. Safety

Labeled safety concerns for Pexeva and Paxil include:

- A Boxed Warning discussing an increased risk of suicidality in children and young adults when antidepressants are used to treat psychiatric disease (antidepressant class labeling)
- Contraindications in patients with known hypersensitivity to the ingredients, those with recent use or current use of monoamine oxidase inhibitors (due to an increased risk of serotonin syndrome), and those using thioridazine or pimozide (due to a drug interaction that increases the concentrations of these concomitant medications, predisposing to torsades de pointes)
- Warnings or Precautions pertaining to suicidality, precipitation of mania, serotonin syndrome (particularly with concomitant use of other serotonergic medications), a potential reduction in the effectiveness of co-administered tamoxifen, akathisia, hyponatremia, an increased risk of bleeding events, an epidemiological association with bone fracture, and potential for acute angle closure glaucoma.

In the clinical program for vasomotor symptoms, a total of 659 patients were treated with paroxetine and 641 patients were treated with placebo. A total of 235 patients in the paroxetine group and 218 patients in the placebo group completed 24 weeks of treatment. These exposures are sufficient in light of the extensive clinical experience with the approved paroxetine products used at higher doses to treat psychiatric conditions.

Major safety findings are described below. Unless noted otherwise, these findings pertain to the pooled data from the one phase 2 trial and two phase 3 clinical trials. The clinical review team identified no concerns based on vital signs and laboratory data.

Deaths: The only death in the paroxetine group involved a 55 year-old woman with cardiac risk factors of hypertension and hyperlipidemia who was reported to have a serious adverse event of coronary artery arteriosclerosis and died of cardiorespiratory arrest about two months into the treatment period. There are no safety concerns for paroxetine based on this isolated death.

Serious adverse events: In the pooled phase 2/3 database, 14 paroxetine-treated patients (2.2%) and nine placebo-treated patients (1.4%) reported at least one serious adverse event. Only the following serious adverse events were reported in more than one paroxetine-treated patient:

- Suicidality: 4/635 (0.63%) paroxetine-treated patients (1 suicide attempt and 3 events of suicide ideation) vs. 0/641 placebo-treated patients. Suicidality is discussed in greater detail below.
- Appendicitis: 2/635 (0.31%) paroxetine-treated patients vs. 0/641 placebo-treated patients. Appendicitis is not a known safety concern for paroxetine or selective serotonin reuptake inhibitors.

The reported serious adverse events do not raise new safety concerns for paroxetine.

Adverse events leading to discontinuation: In the pooled phase 2/3 database, adverse events leading to discontinuation were reported in 4.7% of paroxetine-treated patients and 3.7% of placebo-treated patients. Three paroxetine-treated patients and no placebo-treated patients discontinued due to suicidality (one patient with suicide attempt and two patients with suicidal ideation). Suicidality is discussed in greater detail below. The remaining adverse events leading to discontinuation were reported in only 1-2 paroxetine-treated patients and sometimes occurred at a numerically higher incidence in placebo-treated patients. The reported adverse events leading to discontinuation do not raise new safety concerns for paroxetine.

Common adverse events: In the pooled phase 2/3 database, 50% of paroxetine-treated patients and 47% of placebo-treated patients reported at least one adverse event. The most common adverse events coded to preferred terms of headache (4.6% with paroxetine vs. 4.2% with placebo), fatigue (3.8% with paroxetine vs. 1.7% with placebo) and nausea (3.6% with paroxetine vs. 1.4% with placebo). These findings show that Brisdelle is reasonably well-tolerated and do not raise new safety concerns for paroxetine.

Suicidality: All antidepressants, including Pexeva and Paxil, have a Boxed Warning describing an increased risk of suicidality in children, adolescents and young adults based on short-term studies in major depressive disorder and other psychiatric conditions. Labeling states that these studies did not show an increase in risk of suicidality with antidepressants for users over 24 years of age and that these studies show a reduction in risk with antidepressants in adults 65 years of age and older. Because Brisdelle contains the same active ingredient as that used in Pexeva and Paxil, the Applicant prospectively assessed suicidality in the clinical program. Drs.

Orleans and Soule discuss in detail the results of the two suicidality instruments used in the clinical program as well as the reported adverse events of suicidal ideation and suicidal attempt. In addition, we obtained input from the Division of Psychiatry Products. See the review by Lucas Kempf, M.D. for details. As shown in Dr. Soule's review and as discussed by Dr. Kempf, there is not a clear signal for suicidality with Brisdelle compared to placebo. For example, Dr. Soule shows that overall treatment-emergent suicidality (reflecting both those events reported as adverse events and those captured using the suicidality instruments) occurred in 15 Brisdelle-treated patients compared to 14 placebo-treated patients. There was a report of a suicide attempt in one Brisdelle-treated patient and no completed suicides. However, conclusions are limited because the trials enrolled patients at low risk of suicidality (e.g., patients with a history of suicidal ideation were excluded), one of the suicidality instruments used conservative discontinuation criteria, and event rates were low yielding indeterminate results. Based on all these considerations, Dr. Kempf recommended labeling Brisdelle with the verbatim suicidality class language used for the antidepressants. However, this class labeling focuses on the increased risk of suicidality in children and young adults (a population that is unlikely to need treatment for vasomotor symptoms), has detailed information from a psychiatric population (which is not likely to be representative of the overall population of postmenopausal women seeking treatment for vasomotor symptoms) and involves higher doses of paroxetine than the 7.5 mg dose proposed for vasomotor symptoms. Based on these considerations, we reached agreement with the Division of Psychiatry Products to revise the suicidality language for Brisdelle. The Brisdelle label notes that antidepressants, including selective serotonin reuptake inhibitors, increase the risk of suicidality in children and young adults when used to treat psychiatric conditions. The label then states that there is limited information regarding the risk of suicidality in women who use Brisdelle for the treatment of vasomotor symptoms and recommends monitoring patients for suicidal thoughts and behaviors and discontinuing Brisdelle if there is worsening depression or suicidality.

Other Selected Adverse Events of Interest: Drs. Orleans and Soule also evaluated the extent to which other labeled adverse events for Pexeva and Paxil (e.g., bleeding events, hyponatremia, activation of mania, akathisia) occurred during the Brisdelle development program. Although some of these events were not reported and others occurred at an incidence that was low and comparable to that with placebo, it is not possible to conclusively determine that the 7.5 mg dose of paroxetine is void of such effects. Therefore, these safety concerns have been included in the Brisdelle label.

Withdrawal events: There have been postmarketing reports of adverse events occurring upon (particularly abrupt) discontinuation of paroxetine and other selective serotonin reuptake inhibitors, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, insomnia and hypomania. More recent paroxetine trials have tapered patients down by 10 mg/day at weekly intervals then discontinued treatment when patients were on 20 mg/day for one week. In the Brisdelle trials, patients abruptly discontinued study medication then were assessed for symptoms during the following week. New symptoms were reported in this time period for 17.6% of Brisdelle-treated patients and 13.7% of placebo-treated patients. Some of the adverse events that occurred at a numerically greater incidence with Brisdelle than placebo were similar to those reported following abrupt discontinuation of Paxil and Pexeva, including

headache, anxiety, lethargy and insomnia although differences between treatment groups were small (about 1-3%). Based on similarities between Brisdelle and placebo with regard to these adverse events and the fact that Paxil and Pexeva are only tapered to 20 mg/day before discontinuing therapy, the label will not recommend tapering Brisdelle prior to discontinuing it.

Postmarketing safety findings: Brisdelle is not marketed in any country. At the time of NDA submission, the Applicant included the most recent Periodic Adverse Drug Experience Report (PADER) for Pexeva covering July 2010 through July 2011. In the 120-day Safety Update, the Applicant included the subsequent PADER covering July 2011 through July 2012. The Applicant also included literature searches for published reports involving paroxetine. As discussed by Drs. Orleans and Soule, these PADERs and literature searches did not raise new safety concerns requiring regulatory action (other than labeling that harmonized the Paxil and Pexeva labels) and yielded findings consistent with the known safety profile of paroxetine.

## 9. Advisory Committee Meeting

On March 4, 2013, we convened the Advisory Committee for Reproductive Health Drugs and posed three questions to the panel.

1. Based on the pre-specified analyses, is there sufficient evidence to conclude that paroxetine mesylate is effective in treating moderate to severe vasomotor symptoms (VMS) associated with menopause?

Seven panel members voted 'yes' and seven voted 'no.' Members who voted 'yes' noted that the totality of the evidence supports a modest but real treatment effect and placed more emphasis on the frequency findings compared to the severity findings. Those who voted 'no' mentioned the modest treatment effects, that one of the four co-primary endpoints was not met in the second trial, and that there is uncertainty regarding what the severity findings mean to patients.

2. Based on the pre-specified analyses, is there sufficient evidence to conclude that the change from baseline in VMS frequency is clinically meaningful to women?

Four panel members voted 'yes' and 10 voted 'no.' Several panel members stated that they had difficulty articulating the rationale behind their votes. Members who voted 'yes' considered the findings (e.g., clinical meaningfulness assessment and persistence of efficacy findings) to be useful even though the overall treatment effect was modest. One of the 'no' votes acknowledged that there is a treatment benefit for some patients and that he cannot justify his 'no' vote. Others who voted 'no' noted the large placebo effect and the small treatment difference between groups.

3. "Is the overall risk/benefit profile of paroxetine mesylate acceptable to support approval of this product for the proposed indication?"

Four panel members voted ‘yes’ and 10 voted ‘no.’ Members who voted ‘yes’ noted that there is some evidence of benefit that would be useful for some women and that there is an adequate safety profile, particularly given that the proposed dose is lower than that approved for the psychiatric indications. Those who voted ‘no’ mostly commented on the modest treatment benefit relative to placebo, although some were concerned with the safety profile (e.g., suicidality).

## 10. Pediatrics

This NDA triggers the Pediatric Research Equity Act (PREA) because it provides for a new indication. The Division and the Pediatric Review Committee (PeRC) agree with the Applicant’s request for a full pediatric waiver because vasomotor symptoms due to menopause do not occur in the pediatric population.

## 11. Other Relevant Regulatory Issues

Financial Disclosures: Drs. Orleans and Soule note that none of the investigators who participated in the phase 3 trials reported disclosable information.

Office of Scientific Investigations (OSI): FDA inspected three clinical sites that enrolled a total of 79 patients in the phase 3 trials. For two of these sites, the final classification was NAI (No Action Indicated). A Form FDA 483 was issued at the remaining site (Dr. Kalafer) but I agree with OSI that the findings (e.g., delayed investigator review of sleep diaries, some patients not having documented compensation, uncertainty whether all unused drug was returned to the sponsor, minor discrepancies in the timing of hot flushes between the diary and compliance report) would not impact the efficacy or safety data generated by this site. Based on the inspections, OSI concluded that the data generated from all three sites can be used in support of the indication. See the review by Roy Blay, Ph.D. for details.

Tradename review: The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proprietary name, Brisdelle, within 90 days of today’s approval date and found the name acceptable. See the review by Manizheh Siahpoushan, Pharm.D. for details.

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The language in the Brisdelle label is adapted from the Pexeva label, where appropriate. We worked closely with the Division of Psychiatry Products to ensure that revisions were acceptable based on their expertise with selective serotonin reuptake inhibitors. Key aspects of labeling that is unique to Brisdelle or revised from the Pexeva label include:

- Modified language regarding suicidality, as discussed under the Safety Section of this memorandum
- A Limitation of Use stating that Brisdelle is not indicated for the treatment of any psychiatric condition
- A Contraindication in pregnancy (Category X) because menopausal vasomotor symptoms do not occur during pregnancy and paroxetine can cause fetal harm. In addition, the Pregnancy section of the label was revised to comply with the new Proposed Pregnancy and Lactation Labeling Rule that is undergoing clearance, while remaining in compliance with existing regulations. See the review by Jeanine Best, M.S.N, R.N., P.N.P. for details.
- A Warning and Precaution stating that healthcare providers consider avoiding the concomitant use of Brisdelle and tamoxifen because of uncertainty regarding the impact of Brisdelle on the efficacy of tamoxifen
- The safety data in Section 6 and the efficacy data in Section 14 are limited to findings from the Brisdelle clinical program, except for the Postmarketing Experience section, which includes reported adverse events from Pexeva and Paxil

The carton and container labeling has been revised in accordance with recommendations from DMEPA. See the review by Manizheh Siahpoushan, Pharm.D. for details.

Brisdelle will have a Medication Guide as required for all selective serotonin reuptake inhibitors. The Medication Guide has been revised in accordance with recommendations from the Division of Medical Policy Programs in the Office of Medical Policy. See the review by Twanda Scales, R.N., M.S.N./Ed. for details.

Both the package insert and Medication Guide have been reviewed for potentially inappropriate promotional statements and such statements have been accordingly revised or removed. See the review by Lynn Panholzer, Pharm.D. from the Office of Prescription Drug Promotion for details.

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

Approval

- Risk Benefit Assessment

I agree with all review disciplines that the available data support approval of paroxetine for the treatment of moderate to severe vasomotor symptoms associated with menopause. I also agree with many members of the advisory panel that paroxetine has shown modest efficacy. The pre-specified analyses from the phase 3 trials show that paroxetine results in a statistically significant reduction in the frequency of moderate to severe hot flashes from baseline to Week 4 and Week 12. The median treatment difference was -1.2 to -1.3 fewer moderate to severe hot flashes per day with paroxetine compared to placebo at Week 4 ( $p < 0.0001$ ) and -0.9 ( $p < 0.01$ ) to -1.7 ( $p = 0.0001$ ) fewer moderate to severe hot flashes per day at Week 12. In addition, the

pre-specified secondary endpoint assessing persistence of benefit showed that 48% of paroxetine-treated patients vs. 36% of placebo-treated patients achieved  $\geq 50\%$  reduction from baseline in the frequency of moderate to severe hot flushes at Week 24 (nominal p-value  $< 0.01$ ). This persistent treatment effect is critical given the expectation that women would typically need chronic treatment for vasomotor symptoms. The pre-specified clinical meaningfulness analyses (which take into account an assessment of clinical benefit from the perspective of the trial participants) show responder rates of 50% for paroxetine vs. 37% for placebo at Week 4 (nominal p-value=0.001) and 51% for paroxetine vs. 43% for placebo at Week 12 (nominal p-value=0.055) with regard to a reduction in the frequency of moderate to severe hot flushes. It is reasonable to accept these supportive results along with the totality of the clinical trial data as providing sufficient evidence for efficacy.

Although the treatment effect on the hot flush severity score achieved statistical significance at Week 4 in both Phase 3 trials and Week 12 in one of the Phase 3 trials, this treatment effect (about a 2% decline from baseline relative to placebo) seems very small. However, as previously discussed, there are methodological issues with the assessment of severity (e.g., instances when the severity score increases when one would have expected a decline) that limit my confidence in the assessment and interpretability of Brisdelle's severity results. For this reason, I agree with Dr. Soule and with the advisory panel members who placed greater emphasis on Brisdelle's frequency findings over the severity findings.

An important consideration is whether the modest efficacy of paroxetine offsets the known safety concerns and supports a positive benefit/risk assessment. As noted by Dr. Soule, the Brisdelle clinical trials did not identify new safety concerns for paroxetine. In fact, the lower dose of paroxetine in Brisdelle did not differ much from placebo with respect to reported adverse events. In addition, many of the identified safety concerns with paroxetine (e.g., drug-drug interactions, serotonin syndrome, potential impact on the efficacy of tamoxifen, precipitation of mania) may be avoided to a great extent with appropriate patient selection. The suicidality findings with Brisdelle are inconclusive but it is noteworthy that in a high-risk population (those with psychiatric disease, including depression) using higher doses of paroxetine or other antidepressants, the suicidality concerns pertain to children and young adults, a population that is not likely to be prescribed Brisdelle for the treatment of moderate to severe vasomotor symptoms.

Based on the above considerations, I consider Brisdelle to be a useful and reasonably safe treatment option for postmenopausal women who cannot or do not wish to use hormonal treatment for their moderate to severe hot flushes.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HYLTON V JOFFE  
06/28/2013