

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203752Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	October 12, 2012
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203752
Type of Submission	Original
Applicant	Noven Pharmaceuticals, Inc.
Date of Submission	December 29, 2011
PDUFA Goal Date	October 29, 2012
Proprietary Name / Established (USAN) names	MINIVELLE ETS/17 β - estradiol (E ₂)
Dosage forms / Strength	Transdermal estradiol system (b)(4) 0.0375, 0.050, 0.075 and 0.1 mg/day applied twice weekly
Proposed Indication(s)	Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause
Recommended:	Approval is recommended.

1. Introduction

With this 505(b)(1) original NDA submission, the Sponsor is seeking approval for a new 17 β -estradiol (E₂) transdermal system (ETS), MINIVELLE™, which contains the same active ingredient as the previously approved products Vivelle® (NDA 020323) and Vivelle®-Dot (020538) manufactured by Noven but marketed by Novartis. (b) (4)

The MINIVELLE ETS NDA has a right of cross-reference to both the Vivelle ETS and Vivelle-Dot ETS NDAs. Compared to the Vivelle ETS and Vivelle-Dot ETS, MINIVELLE is a revised ETS with a smaller active surface area (See Table 1), but with the same multipolymeric adhesive platform. The MINIVELLE ETS contains the active component, E₂, in a multi-polymeric adhesive and is designed to release E₂ continuously to intact skin. (b) (4) dosage strengths are sought for the MINIVELLE ETS, to provide nominal doses of (b) (4), 0.0375, 0.050, 0.075 and 0.1 mg per day, which corresponds to an active surface area of (b) (4), 2.48, 3.30, 4.95 and 6.6cm².

Table 1. Size and Dosage Strengths of the Vivelle ETS, Vivelle-Dot ETS and MINIVELLE ETS (Sponsor originally proposed name was (b) (4))

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 ²
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	29 cm ²	10 cm ²	6.60 cm ²
Estradiol Content per 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

No new clinical data was submitted in support of the MINIVELLE ETS. The establishment of safety and efficacy of the MINIVELLE ETS is sought via bridging to the

findings of the Vivelle ETS by evaluation for bioequivalence (BE) supported by data submitted to the NDA. The Vivelle ETS is available in (b) (4) five dosage strengths (b) (4) with the Vivelle ETS having larger surface areas, as noted above.

The Vivelle ETS, Vivelle-Dot ETS, and MINIVELLE ETS all have the same indication (or proposed indication in the case of MINIVELLE), treatment of moderate-to-severe vasomotor symptoms due to menopause. Both the Vivelle ETS and Vivelle-Dot ETS are approved for the prevention of osteoporosis at the 0.025 mg per day dosage strength. As noted previously, approval for the MINIVELLE ETS is sought on the basis of BE to the Vivelle ETS. The Sponsor has not sought an indication for the prevention of osteoporosis.

There were no controversial issues associated with the review of this NDA. Based on the information submitted comprehensive reviews were performed by the review disciplines of Chemistry/Biopharmaceutics, Clinical Pharmacology and Clinical. These reviews, as well as the abbreviated reviews from Preclinical Pharmacology and Statistics, are summarized.

2. Background

NDA 020323 for the Vivelle ETS was *Approved* on October 28, 1994 for the “treatment of moderate to severe vasomotor symptoms associated with menopause”. Approved doses of Vivelle ETS for vasomotor symptoms are 0.0375mg, 0.05 mg, 0.075mg, and 0.1mg per day. Statistically significant improvement versus placebo in **both** the frequency **and** the severity, the co-primary endpoints, for the 0.0375 mg dosage strength was not reached until the 6th week of treatment. This dosage strength was approved with the restrictive language that, “women taking the 0.0375 dosage may experience a delay in the onset of efficacy.” In order to remove this restrictive language, the Sponsor agreed to conduct a Phase 4 study that would define the percentage of patients who received relief of vasomotor symptoms at the lowest dose (0.0375 mg/day). The results of that Phase 4 study were submitted to the Agency on April 30, 1999 in Supplement 021 to NDA 020323. The results demonstrated that for the study group receiving the 0.0375 mg per day dosage strength of the Vivelle ETS, a statistically significant improvement (reduction) vs. the group receiving placebo for **both** the frequency **and** severity of hot flushes at Weeks 4 and 12. The sample size was sufficient to detect a mean difference of greater than or equal to 2.0 hot flushes per day (the clinically meaningful threshold) in the reduction of frequency for the Vivelle ETS vs. placebo. Supplement 021 to remove the restrictive language (regarding delayed onset of efficacy) with the 0.0375 mg per day dose of the Vivelle ETS was approved on February 25, 2000. On August 16, 2000, NDA 020323/Supplement 23 and NDA 021-167 were *Approved* for the 0.025 mg per day dosage strength of the Vivelle ETS for the indication of prevention of postmenopausal osteoporosis in at-risk patients. Noven discontinued the manufacture of the Vivelle ETS in 2006.

NDA 020538 for the Vivelle-Dot ETS, in the same dosage strengths as those approved to that date for the Vivelle ETS, was *Approved* on July 31, 1996. Approval of the Vivelle-Dot ETS was based on the demonstration of bioequivalence to the Vivelle ETS. On January 18, 2001, Novartis submitted NDA 020538/Supplement-014 to remove the restrictive language for the 0.0375 mg per day dose of the Vivelle-Dot ETS. NDA 020538/Supplement 14 was

Approved on May 03, 2002. NDA 020538/Supplement 015 adding the prevention of postmenopausal osteoporosis indication in at-risk patients for the 0.025 mg per day dosage strength of the Vivelle-Dot ETS was also *Approved* on May 03, 2002.

There are many estrogen-alone products, oral (7 originator drug products), transdermal (8 originator drug products), topical (5 originator drug products) and vaginal creams, rings or tablets (5 originator drug products), which have been previously approved for the treatment of moderate to severe vasomotor symptoms due to menopause.

A pre-IND meeting (PIND 076647) was held between the Division of Reproductive and Urologic Products (DRUP) and Noven Pharmaceuticals on September 11, 2007 to discuss the developmental plan for the MINIVELLE ETS. DRUP made the following major recommendations:

- No preclinical studies were necessary if the patch and matrix and the impurities and degradation products of the MINIVELLE ETS were qualitatively and quantitatively similar to the Vivelle ETS and Vivelle-Dot ETS
- A pivotal, single dose, two-way crossover, bioequivalence study comparing the highest strength of the Vivelle ETS (not Vivelle-Dot ETS) to the highest strength of the MINIVELLE ETS would provide support for approval of the MINIVELLE ETS. The Division stated the following with regards to assessment for bioequivalence:
 - The Vivelle ETS should be used as the reference in the study since the clinical trials were conducted with the Vivelle ETS. The Vivelle ETS, at the 0.1 and 0.05 mg per day dosage strengths, was still commercially available at the time of the meeting
 - BE should be based on both baseline corrected and uncorrected relevant pharmacokinetic parameters
 - The BE requirement for the lower strengths of the MINIVELLE ETS could be waived based on information:
 - BE at the highest dose strength
 - Proportionally similar composition (active and inactive ingredients) to the strength of the product for which the same manufacturer had conducted the in vivo BE study
 - Comparable in-vitro dissolution profiles of the MINIVELLE ETS
 - Dose proportionality of the MINIVELLE over the dose range of 0.025 to 0.1 mg per day
- A separate single-dose, crossover study with at least three dosage strengths of the MINIVELLE ETS should be conducted to determine the dose proportionality of the MINIVELLE ETS
- The dermal characteristics (i.e., adhesive properties, skin irritation, and discomfort) of the MINIVELLE ETS should be evaluated in the BE and dose proportionality studies.

On March 18, 2011, DRUP reiterated to Noven Pharmaceuticals that they should conduct a dose proportionality study and advised them on the study design. DRUP further advised that measurement of E₂ and estrone (E₁) would be sufficient. DRUP also indicated that a

full 24-hour baseline measurement of both E₂ and E₁ concentrations should be performed and a standardized adhesion scale should be used to assess adhesion of the MINIVELLE ETS. Both recommendations were incorporated by the Sponsor into their final protocol.

The MINIVELLE ETS for the treatment of moderate to severe vasomotor symptoms due to menopause was submitted on December 29, 2011. The application was administratively filed on February 27, 2011. DRUP issued a 74-day “no filing issues identified” letter on March 09, 2012.

3. CMC/Biopharmaceutics/Device

The drug substance, E₂, is a white to practically white crystal or powder, chemically described as *estra-1,3,5(10)-triene-3,17β-diol*, with a melting point of 173-179°C. It has an empirical formula of C₁₈H₂₄O₂ and a molecular weight of 272.38. The drug substance will be manufactured and packaged at (b) (4). The applicant references DMF (b) (4) for all relevant information pertaining to the manufacture, control and release of the drug substance. DMF (b) (4) was most recently reviewed and deemed adequate on May 24, 2011. No changes to the DMF have been made since the 2011 review and, therefore, DMF (b) (4) is considered adequate to support NDA 203752.

The drug product, MINIVELLE ETS, contains E₂ in a multipolymeric adhesive. The system is designed to release E₂, the active pharmaceutical product (API), continuously upon application to intact skin. The MINIVELLE ETS is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a flexible backing film; 2) an adhesive formulation containing E₂, acrylic adhesive, silicone adhesive, oleyl alcohol (OA), Povidone-(b) (4) and dipropylene glycol (DPG); and 3) a polyester release liner that is attached to the adhesive surface and must be removed before the patch can be used.

In addition to the API E₂, the drug-in-adhesive matrix contains (b) (4) excipients: (b) (4)

(b) (4)

The MINIVELLE ETS is circular in shape and translucent to slightly opaque white. It is manufactured at Noven Pharmaceuticals in Miami, FL. Two additional facilities have been listed for raw material and finished product microbial testing all of which are domestic. It was noted during review, that the maximum storage time for the raw material (b) (4) is (b) (4) from the date of manufacture. Use within (b) (4) prevents the impurity (b) (4) from rising above USP acceptance criterion of (b) (4). The quality of the drug product is controlled by tests for appearance, assay, content uniformity, identification, adhesion, drug release, impurities, cold flow, pouch seal integrity and microbial limits. Each carton will contain eight transdermal systems of a single strength. A 24 month expiration date has been granted (based on 12 months of provided stability data for Vivelles-Dot). The container “Closure System Development of the Drug Product” information presented in the application is adequate.

Inspections of all manufacturing sites were requested through EES. The recommendation from the Office of Compliance (made August 15, 2012) is ACCEPTABLE for the drug product manufacturing and testing sites.

In the PLR formatting of the labeling submitted with the application, there were errors in [REDACTED] (b) (4). The labeling errors were identified in the 74-day filing memorandum. All outstanding errors in the CMC section of Prescriber Information were adequately addressed in Amendments dated, September 12 and November 02, 2011.

The identifying label on the ETS includes the tradename and the strength of each system. The backing print is a random print with qualified ink. Given the small size of the ETS and the low intensity of the print, the Agency made the recommendations (IR letter dated July 19, 2012) to improve the readability of the identifying information by 1.) using a darker/more distinguishable ink color than the currently proposed [REDACTED] (b) (4) 2.) decreasing the number of rows printed per unit and 3.) Remove the [REDACTED] (b) (4) from [REDACTED] (b) (4) if a tradename is not to be used. Noven responded and stated that they will launch the commercial product utilizing a [REDACTED] (b) (4) (newly proposed ink), while completing their qualification and stability work of this more distinguishable ink. The Applicant confirmed that they do not intend to switch between the “[REDACTED] (b) (4) and [REDACTED] (b) (4) because of concern for potential patient confusion. The Sponsor also provided a justification supporting that it was not possible to decrease the number of rows of wording printed per unit. This justification was acceptable.

Per the ONDQA Chemistry reviewer, the NDA is recommended for Approval from a CMC perspective.

The Biopharmaceutics review was focused on:

1. The evaluation and acceptability of the data supporting the proposed in vitro drug release methodology and acceptance criteria.
2. The biowaiver request for the lower strengths of the MINIVELLE ETS.

Regarding the biowaiver request, the Biopharmaceutics review notes that the in vitro drug release profile of each of the lower strengths of the MINIVELLE ETS (0.025, 0.0375, 0.050, and 0.075 mg per day) was compared to the drug release profile of the highest strength (0.1mg per day). The release profiles are similar in shape and meet the criteria for similarity (f1 and f2 factors). Per the Biopharmaceutics reviewer, the results from the BE study and similarity f2 test support Noven’s request for a bioavailability (BA)/BE waiver for the proposed lower strengths of MINIVELLE and, therefore, the biowaiver is granted.

Regarding the in vitro drug release method and acceptance criteria, agreement on the following was reached.

- The following drug release method and acceptance criteria are acceptable on an interim basis

Apparatus	Cylinder Speed	Medium	Volume	Acceptance Criteria
USP Apparatus 6	(b) (4)	Water at 32°C	(b) (4) 900 ml: 0.05 mg/24 hr and 0.075 mg/24 hr, 0.1 mg/24 hr	2 hr: (b) (4) 6 hr: (b) (4) 18 hr: TBD (report value) 24 hr: (b) (4) 36 hr: TBD (report Value) Refer to USP <724> for L1/L2/L2 testing

- The Applicant will collect drug release profile data for the additional 18 and 36 hours time-points for the registration batches starting at the next scheduled stability time-point and for the upcoming validation batches. The extension of the collection period to 36 hrs will ensure that \geq (b) (4) of drug can be consistently achieved
- The Applicant will investigate whether an (b) (4) will result in a higher release rate with $>$ (b) (4) of drug being released in a shorter sampling period, without losing the discriminating ability
- The drug release data collected during the first year from approval date will be used for the setting of the final acceptance criteria
- The collected data and a proposal for the final drug release method and acceptance criteria should be submitted to FDA within fifteen months of the approval date, under a prior approval supplement (PAS) to the NDA
- Upon review of the data provided in the PAS, the drug release methodology and acceptance criteria for MINIVELLE ETS will be finalized.

In submission SDN-012, dated September 17, 2012, Noven confirmed the following commitments:

- In the IR Response dated July 31, 2012 Noven agreed to add drug release sampling timepoints at 18 and 36 hours. The response states, “We agree to collect 18 and 36 hour data starting at the next stability timepoint and for the upcoming validation batches.” Noven further agreed to collect dissolution data including the 18 and 36 hr timepoints for 12 months. Noven agreed that by the end of 15 months, they will submit the dissolution data, proposed acceptance criteria, and justification as a post-approval supplement.
- Noven committed to evaluating the release rate method recommended by the Agency in its IR letter dated, July 12, 2012. The recommended methodology consists of (b) (4) The results

of this evaluation will also be included in the post approval supplement planned for submission in 15 months.

The Biopharmaceutics reviewer found the agreements on the part of Noven Pharmaceuticals to be acceptable and recommends that the MINIVELLE ETS receive approval.

4. Nonclinical Pharmacology/Toxicology

In the September 11, 2007 preIND meeting with Noven Pharmaceuticals, the Agency agreed that no additional preclinical studies for the MINIVELLE ETS were necessary to support marketing. This decision was based on the following:

1. The MINIVELLE ETS patch and matrix materials are the same and the impurities and degradation products are reported qualitatively and quantitatively similar to the Vivelle ETS and Vivelle-Dot ETS. The manufacturing process for the Vivelle-Dot ETS and MINIVELLE ETS is represented by the Sponsor to be very similar.
2. Preclinical studies have shown that the Vivelle-Dot ETS is neither a primary skin irritant nor a dermal sensitizer.
3. The nonclinical pharmacology, pharmacokinetics, and toxicology of 17 β -estradiol delivered via an estradiol transdermal system are well characterized as summarized in the current Package Inserts for the Vivelle ETS and Vivelle-Dot ETS.

Based on the results of the preclinical studies with the Vivelle ETS demonstrating lack of skin irritation in the rabbit and delayed sensitization in guinea pig in addition to the safety profile of the Vivelle ETS in clinical trials, Pharmacology/Toxicology recommends approval of NDA 203752 for the MINIVELLE ETS for treatment of moderate to severe vasomotor symptoms associated with menopause.

5. Clinical Pharmacology/Biopharmaceutics

The Sponsor submitted four Clinical Pharmacology studies including a BE study (Study N28-004) and a dose-proportionality study (Study N28-005). The BE and dose proportionality studies used the to-be-marketed (TBM) formulation. The other two studies submitted to the NDA, Studies N28-001 and N28-003, used previous formulations and were submitted as supportive information. The Office of Clinical Pharmacology (OCP) reviewed the BE and dose proportionality studies conducted with the TBM formulation. The reader is referred to the review of Dr. Chongwoo Yu, OCP, dated August 16, 2012 for a comprehensive review of the BE and dose proportionality studies. The two studies submitted as supportive were not reviewed as they were not conducted with the to-be-marketed formulation and not considered relevant by OCP.

The pivotal BE study, Study N28-004, was conducted with the highest strength of the MINIVELLE ETS developed [1.65 mg E₂ in a 6.6 cm² estradiol transdermal system (ETS) with nominal delivery dose of 0.1 mg per day) compared to the Vivelle ETS (8.66 mg E₂ in a 29 cm² ETS with nominal delivery dose of 0.1mg per day). A biowaiver was sought

for the lower dosage strengths. Study N28-004 was an open-label, single center, single dose, randomized, 2-way crossover study conducted under a fed state (after standardized breakfast) in 100 healthy nonsmoking postmenopausal women 40 to 65 years of age. The inclusion and exclusion criteria for entrance into the study were standard for a pharmacokinetic study in healthy women and were acceptable. In two treatment periods, at 8am (\pm 10 min) on Day 1 and Day 22 (cross over) of the study, each subject received Treatment A (test), a single MINIVELLE ETS applied for 84 hours of treatment, and then Treatment B (reference), a single Vivelle ETS applied for 84, according to the randomization schedule. There was a 17.5 day washout period between the removal of the Treatment A ETS on day 4 (84 hours after application of the first patch on Study Day 1) and the application of the Treatment B ETS on Study Day 22. While on treatment, subjects were allowed to shower, but not to completely immerse themselves in a bath. Subjects were prohibited from using any soap, body lotion, oil, or cream at or around the application site. The application site was not rubbed or disturbed for the period of time inclusive of application to 72 hours following removal. Blood sampling was performed at 24, 22, 20, 18, 16, 12, 10, 8, 4, and 0.5 hours before ETS application, and 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 90, 92, 96, 102, 108, and 120 hours post-dose in each treatment period. ETS were evaluated multiple times for evidence of adhesion to the site of application and discomfort at that site. Application sites were also assessed for adhesive residue remaining on the skin immediately after ETS removal. An assessment for skin irritation was made prior to ETS application and multiple times after removal of the transdermal system.

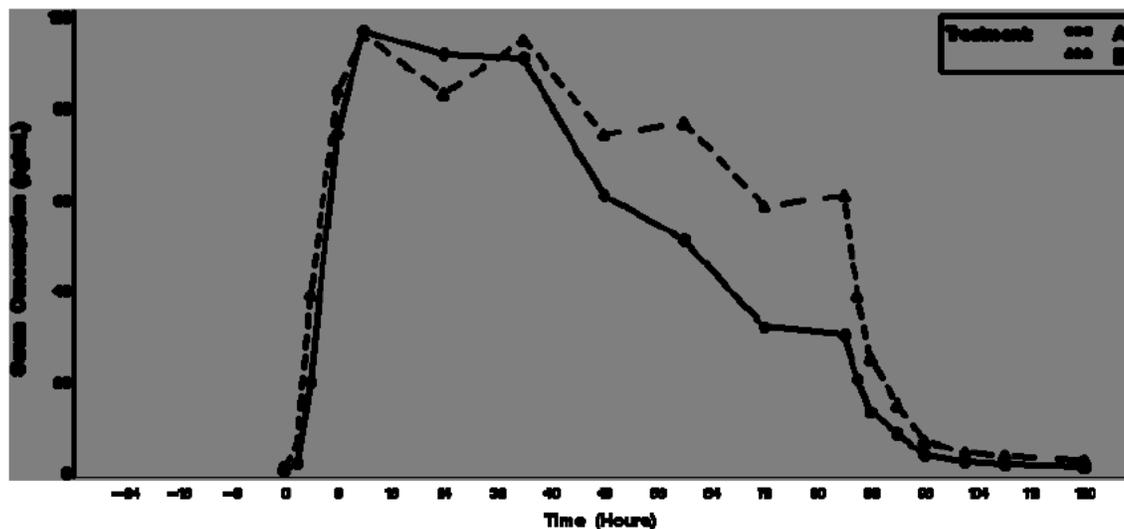
Ninety-nine (99) subjects were randomized and received both treatments. Two subjects did not complete both treatments [Subject 004-01-029 had detachment prior to the 24 hour post dose assessment of Treatment A and Subject 004-01-048 withdrew her consent prior to Treatment B (see Section **8 Safety** of this review for an explanation)]. These two subjects were removed from the analysis. An additional subject (Subject 004-01-063) was excluded from the analysis because of an abnormally high concentration of E_2 at baseline. The OCP reviewer excluded a fourth subject (Subject 004-01-015) for this same reason Serum samples were analyzed for E_2 , unconjugated E_1 , and total E_1 . PK analysis was performed on all three analytes. E_2 was analyzed with and without baseline correction (for endogenous E_2). However, as the goal is to compare the exposure of E_2 by the contribution of the drug products, the baseline corrected E_2 PK parameters were selected for the BE analysis. The clinical team agrees that the baseline corrected PK parameters are more appropriate for the BE analysis. The reader is referred to Dr. Yu's review for a discussion of the E_2 baseline correction. The following PK parameters were calculated for baseline uncorrected E_2 , baseline corrected E_2 , unconjugated E_1 , and total E_1 :

- C_{max} : the maximum serum concentration observed
- AUC_{84} : the area under the serum concentration-time profile; calculated from time 0 to 84 hour (wear time)
- AUC_{last} : the area under the serum concentration-time profile; calculated from time 0 to the last measurable concentration by the linear trapezoidal rule (120 hours post-dose)
- AUC_{inf} : the area under the serum concentration-time profile extrapolated to infinity

- T_{max} : the time of the maximum observed concentration
- k_{el} : elimination rate constant (slope of the log concentration vs. time curve between 84 and 120 hours)
- $t_{1/2}$: elimination half-life ($\ln 2/k_{el}$)

The average concentration-time profiles for baseline-corrected E_2 are presented in **Figure 1**.

Figure 1. Average Baseline-Corrected E_2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (Test: MINIVELLE ETS) And Treatment B (Reference: VIVELLE ETS)



Source: OCP review Figure 4, page 10 and Sponsor Figure11-2 Study Report N28-004

The Sponsor’s baseline and uncorrected BE analyses are presented in Table 2.

Table 2. Sponsor’s Baseline Corrected and Uncorrected BE Analyses of E_2 (N=97)

	AUC ₈₄	AUC ₁₂₀	AUC _{inf}	C _{max}
Baseline Corrected Analysis				
Ratio of LSM ^a	86.4%	84.9%	84.2%	109%
90% geometric CI ^b	81.0-92.2%	79.5-90.6%	78.9-89.8%	103-116%
Baseline Uncorrected Analysis				
Ratio of LSM ^a	87.0%	85.8%	NR ^c	109%
90% geometric CI ^b	81.9-92.5%	80.8-91.1%	NR ^c	103-115%

^a Calculated using least squares means according to the formula: $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$.

^b 90% geometric confidence interval using ln-transformed data.

^c not reported

Source: OCP review Table 4, page 10

The OCP reviewer also performed a BE analysis to confirm the Sponsor’s findings. Results of that analysis are presented in Table 3.

Table 3. Reviewer's Baseline Corrected Analysis of E₂ (N=96)

	AUC ₈₄	AUC ₁₂₀	AUC _{inf}	C _{max}
Ratio of LSM ^a	86.1%	84.5%	84.5%	108.8%
90% geometric CI ^b	80.7-91.7%	79.2-90.3%	79.2-90.3%	102.4-115.6%

^a Calculated using least squares means according to the formula: $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$.

^b 90% geometric confidence interval using ln-transformed data.

Source: OCP review Table 5, page 10

The OCP Reviewer determined that the 90% geometric CIs are within the acceptable BE range for AUC₈₄ and C_{max} but not for AUC₁₂₀ and AUC_{inf}. OCP finds the assessment of AUC₈₄ to be more clinically relevant as the patch was applied for an 84 hour period [the approved labeling states that the ETS should be applied every 3 (72 hours) to 4 days (96 hours)]. Based on the findings for AUC₈₄ and C_{max}, BE at the highest strength of the MINIVELLE ETS is declared.

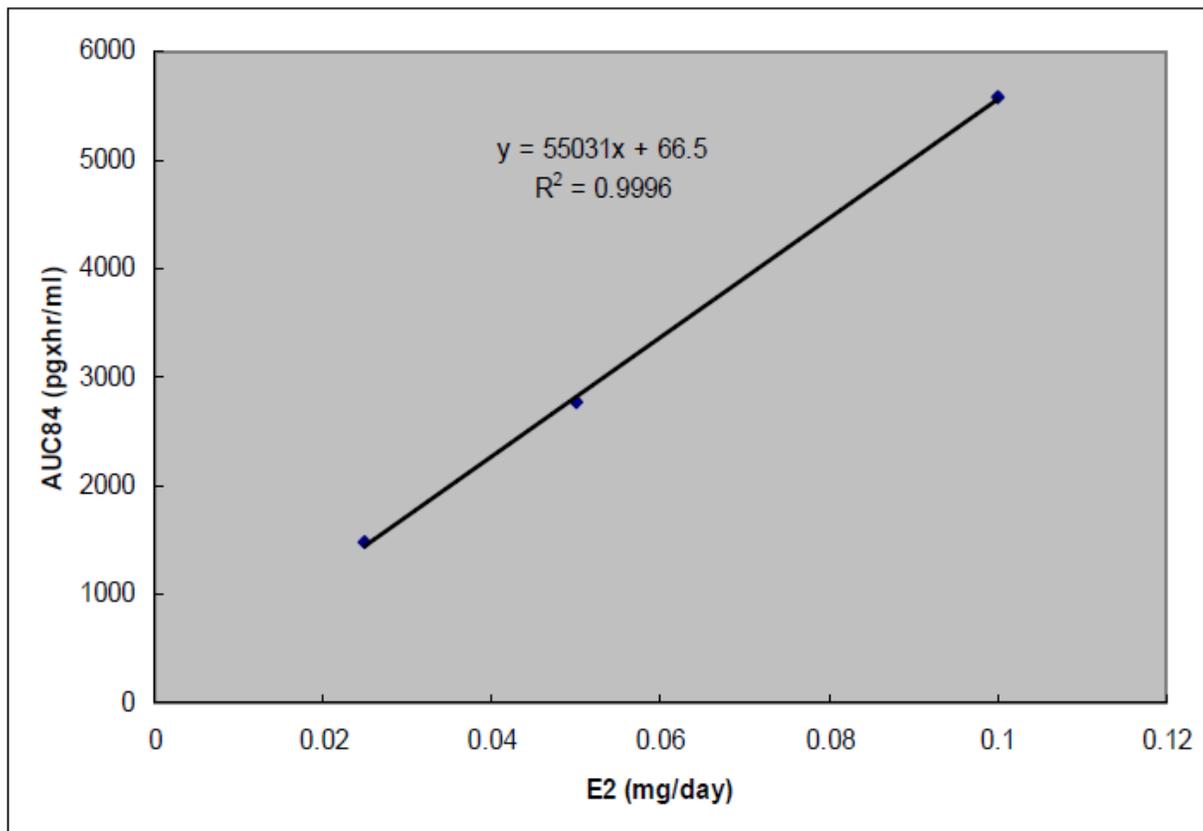
The Sponsor submitted a biowaiver request for the lower dose strengths of 0.025, 0.0375, 0.050, and 0.075 mg per day. The Sponsor supports the biowaiver request based on:

- The establishment of BE of the MINIVELLE ETS to the Vivelle ETS at the highest strength of 0.1 mg per day
- Establishment of dose proportionality over the dose range of 0.025-0.1 mg per day (see dose proportionality discussion below)
- Different doses of MINIVELLE are compositionally proportional (see Section 1 **Introduction** Table 1 of this review)
- *In vitro* dissolution profiles of all strengths of the MINIVELLE ETS are comparable [(f₂ > 50) see Biopharmaceutics discussion under Section 3 **CMC, Biopharmaceutics and Devices**]

The Sponsor conducted and submitted a dose proportionality study, Study N28-005, to support their request for biowaiver for each of the lower dose strengths of the MINIVELLE ETS. The study was a Phase 1, randomized, open-label, single center, single-dose, three-way crossover study of 36 healthy nonsmoking postmenopausal women 40 to 65 years of age. The inclusion and exclusion criteria for entrance into the study were consistent with those used in Study N28-004 with the addition of an exclusion criterion for the use of antihistamines or topical products within 72 hour of initial dosing in the study. The entrance criteria were acceptable. During the three treatment periods, all subjects received Treatment A, a single 0.1 mg per day MINIVELLE ETS applied for 84 hours of treatment; Treatment B, a single 0.05 mg per day MINIVELLE ETS applied for 84 hours of treatment; or Treatment C, a single 0.025 mg per day MINIVELLE ETS applied for 84 hours of treatment according to the randomization schedule. Subjects received their assigned treatment on Day 1, Day 22, and Day 43. There was a minimum 21 day washout period between each of the treatment periods. Blood sampling was on Day 0 (for baseline) at -24, -22, -20, -18, -16, -12, -10, -8, -4 and -0.5 hours pre-dose prior to period 1 and then 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours after treatment administration in each treatment period.

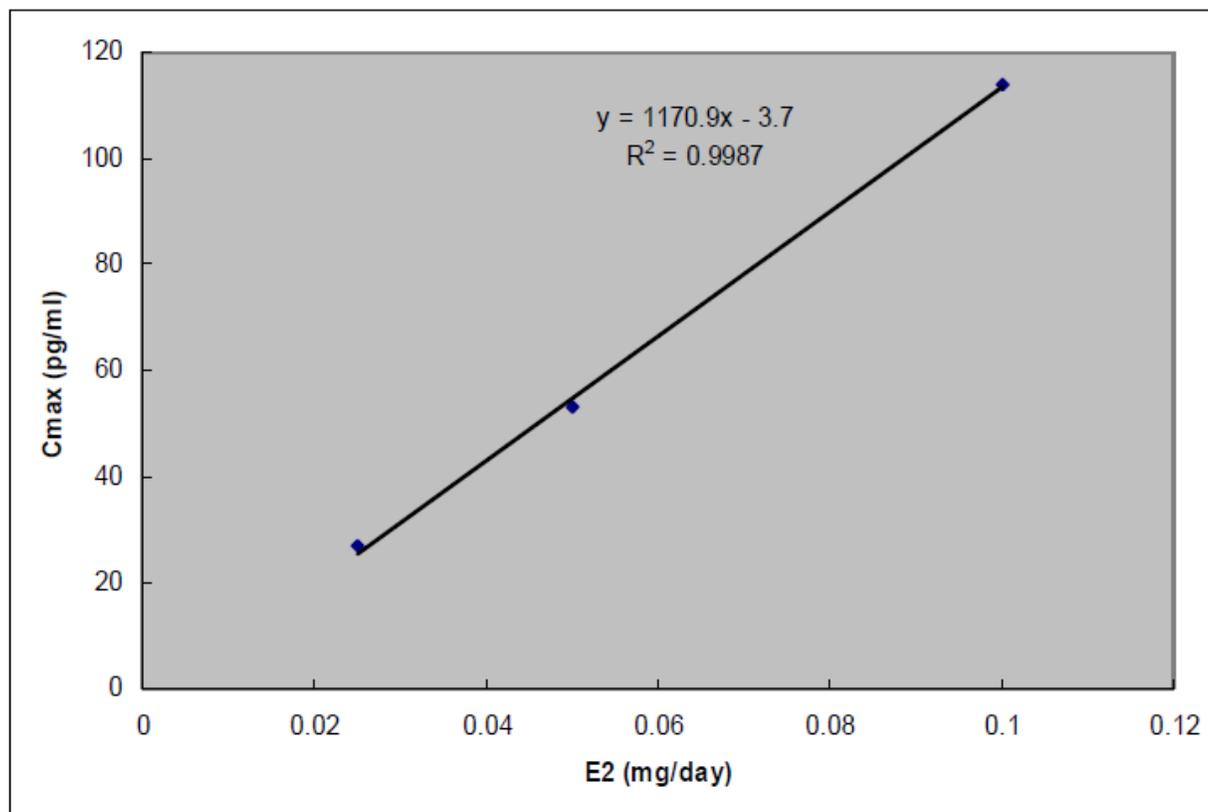
Figures 2 and 3, respectively presents the relationship of the E₂ dose with the E₂ AUC₈₄ or E₂ C_{max}, respectively.

Figure 2. Relationship of dose of E₂ and Mean AUC₈₄ Following a Single Dose of the MINIVELLE ETS in Postmenopausal Women



Source: OCP review Figure 6, page 12

Figure 3. Relationship of the dose of E₂ and Mean C_{max} Following a Single Dose of the MINIVELLE ETS in Postmenopausal Women



Source: OCP review Figure 7, page 13

The E₂ AUC and C_{max} increase linearly with increasing E₂ dose from 0.025mg per day to 0.1 mg per day of the MINIVELLE ETS and dose proportionality is established.

Adherence of the MINIVELLE ETS was assessed based on the combined data from the BE and dose proportionality studies consisting of 208 total observations. Of the 208 MINIVELLE observations, approximately 98 % of the observations had an adhesion score of 0 (i.e., the skin adhesion rate was greater than or equal to 90 percent) over the 84-hour wear period. One subject had a complete detachment during the wear period. Approximately 65 percent of the MINIVELLE ETS evaluated in these studies were with the 0.1 mg per day (6.6 cm² active surface area) dose.

Distribution, metabolism, and excretion of E₂ from MINIVELLE are expected to be the same as those for the Vivelle ETS. The Sponsor is proposing to use the information from the Vivelle ETS for their product.

No new DDI studies were conducted with the MINIVELLE ETS. Noven proposes to use the information from the Vivelle ETS in the MINIVELLE ETS label.

At the request of OCP and DRUP, the Division of Bioequivalence and GLP Compliance (DBGC) conducted audits of the clinical and analytical portion of BE Study N28-004. The

audits were conducted at Elite Research Institute, Inc., Miami, Florida and at (b) (4) during the period of (b) (4)

The audits included a thorough examination of study record, facilities, and equipment as well as interviews and discussions with the firms' management and staff. Following the inspections at the clinical and analytical sites, *no significant* objectionable conditions were observed and Form 483 was not issued.

The OCP review concludes that the information submitted to support NDA 203752 for the MINIVELLE ETS is acceptable provided that a satisfactory agreement is reached regarding labeling.

6. Clinical Microbiology

Not applicable to this NDA.

7. Clinical/Statistical - Efficacy

No new Phase 3 trials for efficacy and safety were submitted with this NDA. Efficacy is bridged to Vivelle by BE. The reader is referred to NDA 020323 for the discussion of the efficacy of the Vivelle ETS. The MOR (Section 6 **Review of Efficacy**) for MINIVELLE, summarizes the Vivelle ETS efficacy data previously submitted in NDA 020323 (for the Approval cycles for the Vivelle ETS) from the 12-week Phase 3 efficacy and safety studies, 1003A, 1003 B and Protocol 036 (Supplement 21). The reader is referred to the MOR for this summary discussion of the efficacy of the Vivelle ETS.

8. Safety

No new Phase 3 trials for efficacy and safety were submitted with this NDA. The labeling for MINIVELLE ETS will have a Section 6 **ADVERSE REACTIONS** that will reflect the clinical trial experience with the Vivelle ETS vs. placebo in the pivotal Phase 3 studies (Studies 1003A, 1003B and Protocol 036) presented in NDA 020323 and the postmarketing experience with the Vivelle ETS. The MOR review for MINIVELLE summarizes the previously reviewed safety profile of the Vivelle ETS derived from the Phase 3 clinical trials presented in the Vivelle ETS NDA 020323. The reader is referred to the MOR (Section 7 **Review of Safety**) of this NDA for this summary discussion of the safety profile of the Vivelle ETS.

Both the BE study, Study N28-004, and dose proportionality study, Study N28-005, were short term studies with total duration of drug exposure between 168 and 252 days. No deaths or serious adverse events occurred while on study drug in either study.

In Study N28-004, during the washout period between treatments, one subject (Subject 004-01-048) experienced first-degree sunburn which resulted in her withdrawal from the study prior to Treatment B. Twenty-six (26) of 100 subjects (26%) experienced a total of 34 treatment emergent adverse events (TEAEs) during Treatment A with the MINIVELLE ETS, while 35 of 99 subjects (35%) experienced a total of 43 TEAEs during Treatment B with the Vivelle ETS. All of the TEAEs were noted to be mild in intensity and most were deemed as "possibly related" to treatment by the investigators. Distribution of TEAEs by

system organ class (see MOR Table 10) and preferred term revealed similar AEs occurring with the MINIVELLE ETS and the Vivelle ETS.

No subject had evidence of skin irritation prior to the start of dosing. It was noted that 35 of 100 subjects (35%) experienced grade 1 erythema (very slight erythema, barely perceptible) and 2 of 100 subjects (2%) experienced grade 2 erythema (definite erythema) with MINIVELLE ETS treatment, while 86 of 99 subjects (87%) experienced grade 1 erythema and 20 of 99 subjects (20%) experienced grade 2 erythema with the Vivelle ETS treatment. The higher rate of skin irritation with the larger Vivelle ETS is not unexpected. The overall skin irritation profile for each treatment was noted as mild and no ETS was removed because of irritation. One subject receiving Treatment A reported discomfort at the 84 hour time point.

In Study N28-005, 11 of 36 subjects (31%) experienced a total of 19 TEAEs during Treatment A (MINIVELLE ETS: 6.6 cm² delivering 0.1 mg per day E₂), as compared to 11 of 36 subjects (31%) experiencing a total of 14 TEAEs during Treatment B (MINIVELLE ETS: 3.3 cm² delivering 0.05 mg per day E₂) and 10 of 36 subjects (28%) experiencing a total of 25 TEAEs in Treatment C (MINIVELLE ETS: [REDACTED] (b) (4) [REDACTED] delivering 0.025 mg per day E₂). All adverse events were mild in severity and most were assessed by the investigator as probably or possibly related to study drug treatment. The distributions by system organ class and preferred term reveal no dose relationship to any drug-related adverse event. The most frequent drug-related adverse events were back pain and lower abdominal pain. Prior to dosing, no evidence of skin irritation was observed in any of the three treatment groups. This was also true at the 84 hour time point (just prior to ETS removal) with the exception of one subject in Treatment B whose skin showed a slightly glazed appearance. Following ETS removal, 92% to 97% of the subjects in each treatment group experienced no or minimal irritation across the remaining time points (85, 96, and 108 hours). Somewhat of a dose response relationship was seen in the incidence of mild skin irritation (grade 1 erythema) at the 85-hour time point with 30.6%, 22.2 % and 25.0 % of subjects receiving Treatment A; Treatment B and Treatment C, respectively exhibiting the response. Similarly at the 96 hour time point, grade 1 erythema was reported by 25.0%, 22.2 % and 13.9 % of subjects receiving Treatment A, Treatment B and Treatment C, respectively. Grade 1 erythema was reported at 108 hour time point by 8.3%, 13.9 % and 11.1 % of subjects receiving Treatment A, Treatment B and Treatment C, respectively. Grade 2 erythema was only seen at the 85 hour time point (just after ETS removal) and was observed in 2 of 36 (5.6%), 3 of 36 (8.3%), and 1 of 36 (2.8%) subjects in Treatment A, Treatment B, and Treatment C, respectively. There were no subjects in any treatment group with Grade 3 or higher (papules, edema, vesicular eruption or strong reaction spreading beyond the test site) or who had an ETS removed due to unacceptable irritation. Across all time points, subjects in Treatment B and Treatment C reported no discomfort. For Treatment A, there were two subjects (01-022 and 01-031) who reported mild discomfort.

Overall there were no new safety concerns generated in the course of observation for these two (BE and dose-proportionality) short term studies. From a clinical perspective, Approval of the MINIVELLE ETS for the “treatment of moderate to severe vasomotor symptoms due to menopause” is recommended based on bridging to the findings of the

Vivelle ETS through the establishment of BE of the MINIVELLE ETS to the Vivelle ETS as well as dose and compositional proportionality and comparable dissolution profiles of the dosage strengths of the MINIVELLE ETS.

9. Advisory Committee Meeting

Advisory Committee input was not sought for the decision on this supplement.

10. Pediatrics

A full pediatric waiver for ages 0-18 was requested by Noven Pharmaceuticals with the rationale that the condition (menopause) does not apply to children. DRUP concurs with the Sponsor's assessment. Noven's request for a full pediatric waiver for the MINIVELLE ETS was discussed at the September 19, 2012 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) subcommittee meeting. The committee determined that the MINIVELLE application did not trigger PREA and, therefore, the Sponsor should be notified that the provisions of PREA are inapplicable to MINIVELLE. The notification to the Sponsor will be included in the action letter.

11. Other Relevant Regulatory Issues

Form FD 3454, dated December 23, 2011 was signed by Sean Russell, the Associate Director, Regulatory Affairs for Noven Pharmaceuticals. Per the applicant, each principal investigator in the study disclosed no "proprietary interest in this product or a significant equity in the sponsor", as defined in 21 CFR 542(b).

12. Labeling

As of the finalization and entry of this review, final agreement on labeling has not been reached. Estrogen class labeling will apply. The label has undergone one round of editing changes and review between DRUP and the Sponsor. The internally acceptable edits from the Division of Professional Drug Promotion (DPDP), Office of Prescription Drug Promotion (OPDP) on the Prescriber Information and the Division of Medical Policy Programs (DMPP) on the Patient Package Insert and Instructions for use have been sent to Noven for final agreement. Once final agreement on the Prescriber Information and Patient Information labeling has been reached, an addendum to this CDTL memorandum will be archived.

ONDQA has accepted the container and carton labeling.

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the Biopharmaceutics, Chemistry, Clinical Pharmacology and Clinical Reviewers that NDA 203752 for MINIVELLE should receive Approval pending final agreement between the Agency and Noven Pharmaceuticals on labeling, specifically the Prescriber Information and Patient Information.

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

/s/

SHELLEY R SLAUGHTER
10/24/2012

Cross-Discipline Team Leader (CDTL) Review Addendum

Date	October 29, 2012
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203752
Type of Submission	Original
Applicant	Noven Pharmaceuticals, Inc.
Date of Submission	December 29, 2011
PDUFA Goal Date	October 29, 2012
Proprietary Name / Established (USAN) names	MINIVELLE ETS/17 β -estradiol (E ₂)
Dosage forms / Strength	Transdermal estradiol system (b) (4) 0.0375, 0.050, 0.075 and 0.1 mg/day applied twice weekly
Proposed Indication(s)	Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause
Recommended:	Approval is recommended.

Final Labeling

As of the finalization and archiving of the original CDTL review of NDA 203752 for the MINIVELLE ETS on October 24, 2012, the labeling negotiations with the Sponsor were ongoing. This addendum to the CDTL review addresses the final agreed upon labeling with the Sponsor.

The PLR formatted Prescribing Information is based on “Estrogen Class” labeling and includes specific class recommendations for the content of the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and **FULL PRESCRIBING INFORMATION** with respect to the **Boxed Warning**, section **4. CONTRAINDICATIONS**, section **5. WARNINGS and PRECAUTIONS** and section **14. CLINICAL STUDIES**, subsections **14.2 Women’s Health Initiative Studies** and **14.3 Women’s Health Initiative Memory Study**.



Section 6. ADVERSE REACTIONS subsection 6.1 **Clinical Trials Experience** presents data from the clinical trials with the Vivelle ETS along with explanatory statements that, “there were no clinical trials conducted with MINIVELLE” and “MINIVELLE is bioequivalent to Vivelle.” No subsection 6.2 Postmarketing Experience was included because the Sponsor did not have access to the postmarketing information for Vivelle, which was marketed by Novartis and there is no postmarketing information on MINIVELLE.

Section 12. **CLINICAL PHARMACOLOGY** subsection **12.3 Pharmacokinetics** includes information that the MINIVELLE ETS is bioequivalent to the Vivelle ETS. Also presented in this subsection are a table and a figure presenting data following a single dose administration of the MINIVELLE ETS from the dose proportionality study. Table 2 presents the mean serum pharmacokinetic parameters of baseline uncorrected estradiol. Figure 1 presents the mean baseline uncorrected estradiol serum concentration time profiles of the 0.025 mg per day, 0.050 mg/day and 0.1 mg per day dosage strengths of the MINIVELLE ETS.

Section 14. **CLINICAL STUDIES**, subsections **14.1 Effects on Vasomotor Symptoms** was edited to update the descriptive language to align as closely as possible to the current presentation of efficacy data from clinical trials for vasomotor symptoms and to clarify the number of trials involved.

The **Patient Information** also reflects recommendations based on “Estrogen Class” labeling. Both the **Patient Information** and **Instructions for Use** included recommendations from the Division of Medical Policy Programs to include language and Figures that are understandable at an 8th grade educational level.

The final agreed upon PRESCRIBING INFORMATION and Patient Information are appended to this review.

Final container and carton labels recommendations were based on input from the Office of New Drug Quality Assurance (ONDQA), Office of Safety Evaluations, Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP).

Conclusions/Recommendations

I concur with the Biopharmaceutics, Chemistry, Clinical Pharmacology and Clinical Reviewers that NDA 203752 for MINIVELLE should receive Approval.

Attachment – Prescribing Information, Patient Information and Instructions for Use

32 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SHELLEY R SLAUGHTER
10/29/2012