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***APPLICATION NUMBER:***

**203752Orig1s000**

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Hylton V. Joffe, M.D., M.M.Sc. |
| **Subject** | Division Director Summary Review |
| **NDA/BLA # Supplement #** | NDA 203752 |
| **Applicant Name** | Noven Pharmaceuticals, Inc. |
| **Date of Submission** | December 29, 2012 |
| **PDUFA Goal Date** | October 29, 2012 |
| **Proprietary Name / Established (USAN) Name** | Minivelle (Estradiol transdermal system) |
| **Dosage Forms / Strength** | Transdermal patch applied twice weekly, delivering 0.0375, 0.05, 0.075, and 0.1 mg/day |
| **Proposed Indication(s)** | Treatment of moderate to severe vasomotor symptoms associated with the menopause |
| **Action/Recommended Action for NME:** | *Approval* |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Phill Price, M.D. |
| Statistical Review | Xin Fang, Ph.D. and Mahboob Sobhan, Ph.D. |
| Pharmacology Toxicology Review | Krishan Raheja, D.V.M, Ph.D. and Alex Jordan, Ph.D. |
| CMC Review | Caroline Strasinger, Ph.D. and Terrance Ocheltree, Ph.D. |
| Biopharmaceutics | Tapash Ghosh, Ph.D. |
| Clinical Pharmacology Review | Chongwoo Yu, Ph.D. and Myong-Jin Kim, Pharm.D. |
| OPDP | Melinda McLawhorn, Pharm.D., BCPS and Carrie Newcomer, Pharm.D. |
| OSI | Jyoti Patel, Ph.D. and Gopa Biswas, Ph.D. |
| CDTL Review | Shelley R. Slaughter, M.D., Ph.D. |
| OSE/DMEPA | Walter Fava, R.Ph, M.S.Ed. and Zachary Oleszczuk, Pharm.D. |
| SEALD | Abimbola Adebowale, Ph.D. and Laurie Burke, M.D. |
| Division of Medical Policy Programs | LaShawn Griffiths, RN, MSHS-PH, BSN and Melissa Hulett, RN, BSN, MSBA |

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
SEALD=Study Endpoints and Labeling Development
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

# Signatory Authority Review

## 1. Introduction

Minivelle is a new transdermal system designed to continuously release 17β-estradiol when applied to intact skin. Noven, the applicant, has submitted a 505(b)(1) New Drug Application (NDA) seeking approval of Minivelle for the treatment of moderate to severe vasomotor symptoms associated with the menopause. This document serves as the decisional memorandum for the application.

## 2. Background

Vivelle (NDA 020323) is an estradiol transdermal system indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause and for the prevention of postmenopausal osteoporosis. Phase 3 trials have confirmed the efficacy and safety of Vivelle for the treatment of moderate to severe vasomotor symptoms at doses (shown as the nominal delivery rate of estradiol per day) of 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. The 0.025 mg/day dose of Vivelle was approved as the starting dose for the prevention of postmenopausal osteoporosis. Efficacy of the 0.025 mg/day dose for the treatment of vasomotor symptoms has not been established. Vivelle is still approved but is no longer marketed or distributed.

Vivelle-Dot (NDA 020538) is an estradiol transdermal system that was approved based upon demonstration of bioequivalence to Vivelle. Vivelle-Dot delivers the same daily dose of estradiol as Vivelle but does so from a smaller active surface area. Vivelle-Dot is currently marketed for the same indications as Vivelle. Novartis is the holder for both the Vivelle and Vivelle-Dot NDAs.

Noven has now developed Minivelle, an estradiol transdermal system that is smaller than Vivelle-Dot (Table 1). Noven is seeking an indication only for vasomotor symptoms based upon a demonstration of bioequivalence to Vivelle. Noven has a right of reference to both the Vivelle and Vivelle-Dot NDAs.

Minivelle is applied twice weekly to the skin of the lower abdomen or buttocks. The proposed dosage strengths are (b) (4) 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

**Table 1. Patch Size (in $cm^2$) for Vivelle, Vivelle-Dot and Minivelle**

| Strength (mg/day) | Vivelle | Vivelle-Dot | Minivelle |
|---|---|---|---|
| 0.025 | 7.25 | 2.5 | (b) (4) |
| 0.0375 | 11 | 3.75 | 2.48 |
| 0.05 | 14.5 | 5.0 | 3.30 |
| 0.075 | 22 | 7.5 | 4.95 |
| 0.1 | 29 | 10 | 6.60 |

## 3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) reviewers recommend approval. See the review by Dr. Caroline Strasinger for further details. Per Dr. Strasinger, the applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product. The drug substance, estradiol, is identical to the drug substance in Vivelle and Vivelle-Dot. (b) (4)

The Office of Compliance has issued an "Acceptable" recommendation for the manufacturing facilities. The applicant will be granted a 24-month expiration date based on 12 months of provided stability data and supporting Vivelle-Dot data.

## 4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers recommend approval based on adequate supportive non-clinical pharmacology/toxicology data in the Vivelle and Vivelle-Dot NDAs. The Minivelle NDA does not contain new non-clinical pharmacology/toxicology data. See the review by Dr. Krishan Raheja for further details.

## 5. Clinical Pharmacology/Biopharmaceutics

The applicant submitted results from two clinical pharmacology studies that used the to-be-marketed formulation of Minivelle. These studies are summarized briefly below. See the clinical pharmacology review by Dr. Chongwoo Yu for further details.

Study N28-004 is the pivotal bioequivalence study. The clinical and analytical sites were inspected by the Office of Scientific Investigations and the data were found to be acceptable. See the review by Drs. Jyoti Patel and Gopa Biswas for further details. This open-label, randomized, cross-over study compared Minivelle to Vivelle in healthy postmenopausal women. Each patch was applied for 84 hours (3.5 days) with a washout period of 17.5 days. The applicant compared the highest to-be-marketed dose of Minivelle to the highest approved dose of Vivelle, both of which nominally deliver 0.1 mg of estradiol per day. A total of 100 women were randomized.

I agree with the clinical pharmacology reviewers that the tested dose of Minivelle is bioequivalent to the tested dose of Vivelle based on the area under the time-concentration curve $(AUC)_{84hr}$ and Cmax. For these parameters, the standard bioequivalence criteria (90% confidence interval 80-125%) are met regardless of whether the baseline estradiol is corrected or uncorrected for endogenous estradiol concentrations (Table 2). The $AUC_{120hr}$ and $AUC_{inf}$ results are qualitatively similar to the results for $AUC_{84hr}$ although some of the results for $AUC_{120hr}$ and $AUC_{inf}$ do not meet the bioequivalence criteria based on the lower bound of the 90% confidence intervals (78.9-79.5%, which is below the 80% cutoff). Because Minivelle

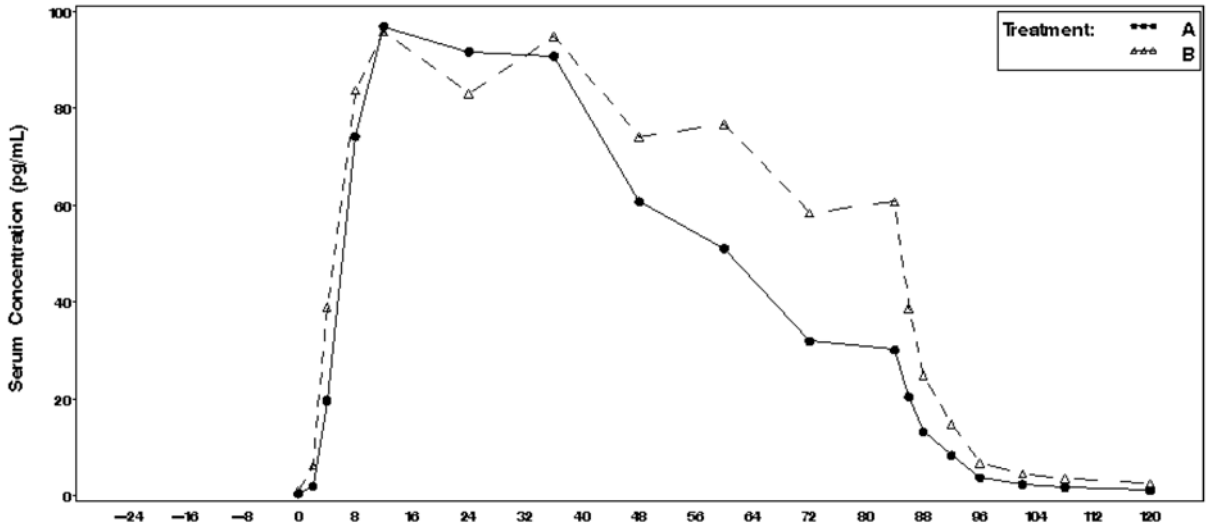
and Vivelle were removed after 84 hours, I agree with Dr. Yu that $AUC_{84h}$ is more appropriate than $AUC_{120hr}$ or $AUC_{inf}$ for assessing bioequivalence. Ideally, participants in the study should have worn the patches for 96 hours (4 days) rather than 84 hours because these patches are intended for use up to 4 days.

**Table 2. Pivotal bioequivalence study showing estradiol exposures with Minivelle 0.1 mg/day relative to estradiol exposures with Vivelle 0.1 mg/day (adapted from Tables 4 and 5 from Dr. Yu's review)**

| | $AUC_{84hr}$ | $AUC_{120hr}$ | $AUC_{inf}$ | $C_{max}$ |
|---|---|---|---|---|
| Baseline uncorrected: Applicant (n=97) | 87.0 (81.9-92.5) | 85.8 (80.8-91.1) | Not reported | 109 (103-115) |
| Baseline corrected: Applicant (n=97) | 86.4 (81.0-92.2) | 84.9 (79.5-90.6) | 84.2 (78.9-89.8) | 109 (103-116) |
| Baseline corrected: Dr. Yu (n=96) | 86.1 (80.7-91.7) | 84.5 (79.2-90.3) | 84.5 (79.2-90.3) | 109 (102-116) |
| Least square means with ln-transformed 90% geometric confidence intervals | | | | |

Figure 1 shows that the Minivelle and Vivelle pharmacokinetic exposures are most similar during the first 2 days of patch wear with larger differences thereafter. This figure shows the baseline-corrected estradiol data. The baseline-uncorrected data are similar.

**Figure 1. Mean baseline-corrected estradiol concentration-time profiles for Minivelle (A, closed circles) and Vivelle (B, open triangles)**




The applicant also conducted a dose proportionality study (N28-005) to support a biowaiver request for the dosage strengths below 0.1 mg/day. In this open-label, three-way crossover study, 36 healthy postmenopausal women were randomized to Minivelle 0.1 mg/day (the highest proposed dose), Minivelle 0.05 mg/day and Minivelle 0.025 mg/day (b) (4) Each patch was worn for 84 hours with a 17.5 day washout period between treatments. As discussed by Dr. Yu, this study adequately demonstrated dose-proportionality.

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