CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203752Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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

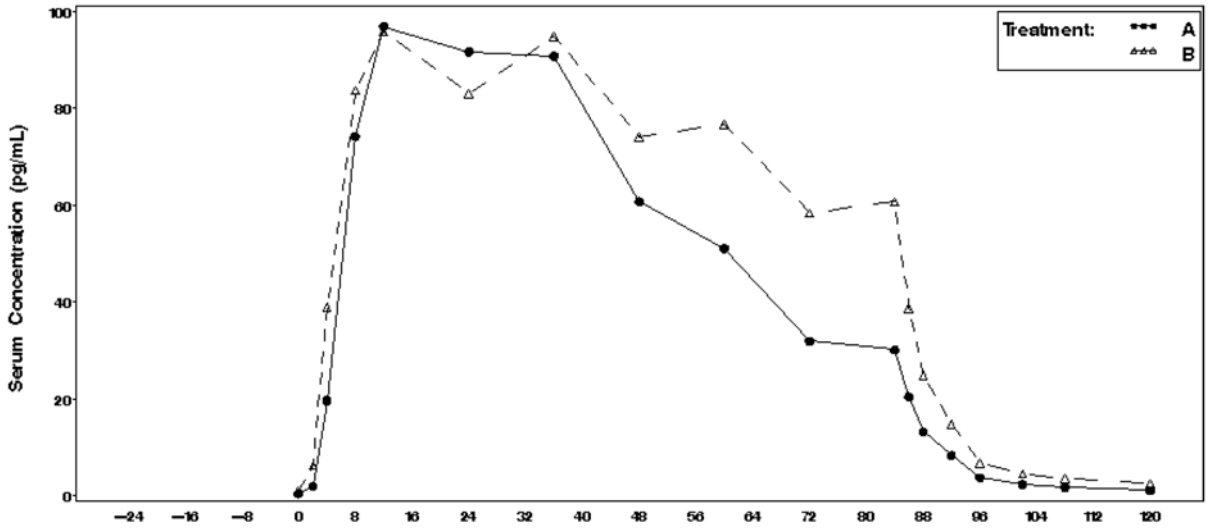
and Vivelle were removed after 84 hours, I agree with Dr. Yu that AUC_{84h} is more appropriate than AUC_{120hr} or AUC_{inf} for assessing bioequivalence. Ideally, participants in the study should have worn the patches for 96 hours (4 days) rather than 84 hours because these patches are intended for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

The applicant has also provided adequate data to show proportional composition and comparable *in vitro* dissolution profiles for all Minivelle strengths. Based on these data, the biopharmaceutics reviewers agree to grant the applicant a biowaiver for the lower proposed Minivelle doses (b) (4) 0.0375 mg/day, 0.05 mg/day, and 0.075 mg/day). See the review by Dr. Tapash Ghosh for further details.

6. Clinical Microbiology

This NDA does not contain clinical microbiology data.

7. Clinical/Statistical-Efficacy

This NDA does not contain new clinical data beyond the data contained in the clinical pharmacology studies. Based on the clinical pharmacology and biopharmaceutics data described above, the applicant is able to bridge to the efficacy data from the Vivelle NDA. See the clinical review by Dr. Phill Price and the Cross-Discipline Team Leader memorandum by Dr. Shelley Slaughter for further details.

8. Safety

Based on the clinical pharmacology and biopharmaceutics data described above, the applicant is also able to bridge to the safety data from the Vivelle NDA. Dr. Price and Dr. Slaughter summarize the safety data derived from the Minivelle clinical pharmacology studies, including skin-related adverse events. I agree with Drs. Price and Slaughter that no new safety concerns were identified for Minivelle based on these limited data.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee.

10. Pediatrics

In consultation with the Pediatric Review Committee (PeRC), we determined that this NDA does not trigger the Pediatric Research Equity Act (PREA) because it does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. We will inform the applicant in the approval letter that this NDA is exempt from this requirement.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) approved the trade name Minivelle within 90 days of today's action date. See the review by Walter Fava for details.

There are no unresolved regulatory issues.

12. Labeling

Upon our request during the review cycle, the applicant has agreed to launch the product using a more distinguishable ink (b) (4) on the transdermal system than originally proposed. The Chemistry reviewers find it acceptable for the applicant to complete their qualification and stability work for this ink while it is being used on the marketed product. See Dr. Strasinger's review for further details.

Key aspects of the physician labeling include the following. See the review by Dr. Slaughter for additional details.

- Compliance with the Physician's Labeling Rule (PLR) format
- Class labeling for estrogen-related safety concerns
- (b) (4)
- Clarifying text that Minivelle is bridged to the efficacy and safety data for Vivelle based on clinical pharmacology and biopharmaceutics data and that there are no additional clinical data with the Minivelle product

The Division of Medical Policy Programs reviewed the patient labeling (Patient information and Instructions for Use) and provided revisions to improve readability. See the review by LaShawn Griffiths and Melissa Hulett for details.

DMEPA reviewed the carton and container labeling and provided several revisions to improve readability and reduce the likelihood of medication error. See the review by Walter Fava for further details.

The Office of Prescription Drug Promotion (OPDP) has reviewed all labeling. Several revisions were made to text that appeared inappropriately promotional. See the review by Dr. Melinda McLawhorn for details.

The Study Endpoints and Labeling Development (SEALD) group conducted a Selected Requirements of Prescribing Information (SRPI) review and identified several formatting deficiencies. We have incorporated all of their recommendations into the final package insert except for the following:

- SEALD requested that we reduce the length of the Boxed Warning in Highlights from 22 lines to 20 lines. However, the current text is identical to class labeling that exists in approved PLR labels for other hormonal therapies and this text has previously been found to be acceptable by SEALD. On further discussion, SEALD accepted this rationale and agreed to this exception.
- SEALD recommended that we remove the term "Vivelle" from the package insert and instead use text such as "another approved transdermal estradiol product". However, by using the term "Vivelle" it is clear to the reader that the comparator data are derived from Vivelle and not from Vivelle-Dot, which is another approved transdermal estradiol product. SEALD deferred the final decision on this issue to the Division. Based on the rationale above, we will maintain the term "Vivelle" in the package insert.

In summary, all labeling issues have been satisfactorily addressed.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval.

- Risk Benefit Assessment

  Phase 3 clinical trials have previously established the efficacy and safety of the 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day doses of Vivelle for the treatment of moderate to severe vasomotor symptoms due to the menopause. In the current NDA, the applicant has successfully bridged Minivelle to the clinical efficacy and safety data of Vivelle via clinical pharmacology and biopharmaceutics data. No new safety concerns were identified with Minivelle based on the clinical data derived from the clinical pharmacology studies. (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None.

- Recommendation for other Postmarketing Requirements and Commitments

  None. The initial biopharmaceutics review requested that several postmarketing commitments be established. However, formalized postmarketing commitments were no longer requested after further discussions were held between the biopharmaceutics reviewers and the applicant. See the reviews by Dr. Tapash Ghosh.

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/s/

HYLTON V JOFFE
10/29/2012