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APPLICATION NUMBER:

203752Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Biopharmaceutics Review Addendum
Office of New Drug Quality Assessment

NDA	203-752 (SDN-012)
Applicant:	Noven Pharmaceuticals, Inc.
Tradename:	Minivelle (estradiol) Transdermal System
Stamp Dates	9/17/12
Established Name:	17β-estradiol (E2)
Dosage Form:	Transdermal Patch
Route of Administration:	Topical
Strength(s), and Dosing Regimen:	0.1, 0.075, 0.05, 0.0375, (b) (4) mg/day; twice weekly
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Reviewer	Tapash Ghosh, Ph.D.

SYNOPSIS

Submission: This is an addendum to the original Biopharmaceutics review for NDA 203-752 for Minivelle (estradiol) Transdermal System (*see Biopharmaceutics review by Dr. Tapash Ghosh dated August 20, 2012, in DARRTS*).

The following comments were included in that original review and were discussed subsequently with the Applicant in a tele-conference held on September 11, 2012. This addendum captures the Applicant's acknowledgment and agreement on these issues as submitted officially under SDN-012 on September 17, 2012.

1. In Vitro Drug Release Method and Acceptance Criteria

- 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 also 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

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collection period to 36 hrs will ensure that (b) (4) of drug can be consistently achieved.

- The Applicant will also 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 loosing 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 from 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 TDS will be finalized,

Review: In the official submission SDN-012 dated September 17, 2012, the Applicant confirmed the following commitments:

- *In the IR Response dated 31-Jul-2012 Noven agreed "to add drug release sampling timepoints at 18 and 36 hours." "We agree to collect 18 and 36 hour data starting at the next stability timepoint and for the upcoming validation batches." Noven further agrees to collect dissolution data including the 18 and 36 hr timepoints for 12 months. By the end of 15 months, Noven will submit the dissolution data, proposed acceptance criteria, and justification as a postapproval supplement.*

- *Noven commits to evaluating the release rate method suggestion provided by the Agency in the IR dated 13-Jul-2012. This consists of* (b) (4) (b) (4) *The results of this evaluation will also be included in the post approval supplement planned for submission in 15 months.*

Reviewer's Comment: The above agreements are acknowledged by the reviewer and are acceptable.

Recommendation: The Applicant's commitments described above will be revisited upon submission of their responses 15 months from the time of approval. Overall, from the Biopharmaceutics perspective, NDA 203-752 for (b) (4) different strengths of Minivelle (estradiol) Transdermal System is recommended for APPROVAL.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

TAPASH K GHOSH
09/18/2012

ANGELICA DORANTES
09/18/2012

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Biopharmaceutics Review
Office of New Drug Quality Assessment

NDA	203-752 (000)
Applicant:	Noven Pharmaceuticals, Inc.
Tradename:	Minivelle (estradiol) Transdermal System
Stamp Dates	12/29/11; 4/27/12; 6/11/12; 7/31/12
Established Name:	17β-estradiol (E2)
Dosage Form:	Transdermal Patch
Route of Administration:	Topical
Strength(s), and Dosing Regimen:	0.1, 0.075, 0.05, 0.0375, (b) (4) mg/day; twice weekly
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Reviewer	Tapash Ghosh, Ph.D.

SYNOPSIS

Submission: On 12/29/2011, Noven Pharmaceuticals submitted NDA 203-752 seeking approval of Minivelle (17β-estradiol [E2]) Transdermal System for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause with a right of cross-reference to NDA 20-323 Vivelle (approved on 10/28/1994) and NDA 20-538 for Vivelle-Dot (approved on 7/31/1996) from Novartis. Vivelle and Vivelle-Dot are E2 transdermal systems manufactured by Noven Pharmaceuticals Inc. and marketed by Novartis. Minivelle is a revised formulation with a smaller active surface area compared to the approved products Vivelle and Vivelle-Dot.

(b) (4) dosing strengths of Minivelle are proposed to provide nominal doses of (b) (4), 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via the skin. Each corresponding system has an active surface area of (b) (4), 2.48, 3.30, 4.95, or 6.6 cm^2 and contains (b) (4), 0.62, 0.83, 1.24, or 1.65 mg of E2 USP, respectively.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the data supporting: (1) the proposed in vitro drug release methodology and acceptance criteria, and (2) the biowaiver request for the lower strengths of Minivelle Transdermal System.

SUMMARY OF FINDINGS AND CONCLUSIONS

The safety and efficacy of Minivelle was bridged from Vivelle via a bioequivalence (BE) study using the highest strength of the proposed Minivelle and the approved Vivelle transdermal systems (***Study N28-004: Single-dose, 2-way crossover BE study in 100 healthy, nonsmoking postmenopausal women***).

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