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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/17β- 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 17β-estradiol (E_2) 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, E_2, in a multi-polymeric adhesive and is designed to release E_2 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 6.6cm^2.

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 E_2 and estrone (E_1) would be sufficient. DRUP also indicated that a

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