

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 20-323/S-021**

**MEDICAL REVIEW(S)**

1999

Medical Officer's Summary of NDA 20-323

1. NDA 20-323-S021  
M.O. Review #1

Submission Date: April 30, 1999  
Review Completed: November 30, 1999

Drug: Estradiol transdermal system

Generic name: 17-Beta Estradiol

Trade name: Vivelle®

Chemical name: Estradiol USP (estra-1,3,5, (10)-triene-3, 17B

Sponsor: Novartis Pharmaceuticals Corporation  
59 Route 10  
East Hanover, New Jersey 07936-1080

Pharmacologic Category: Estrogen

Clinical Indication: Estrogen Replacement Therapy

Dosages and route of Administration: 0.0375 mg per day, 0.05 mg per day, 0.075 mg per day, and 0.1 mg per day

NDA Drug Class:

Related Drugs: Approved estradiol transdermal patches are Estraderm®, Climara®, Vivelle®, Menorest®, and Alora®.

**Summary/Issues**

This 26-volume submission from Novartis contains one well-designed placebo controlled study to support Vivelle in the treatment of moderate to severe vasomotor symptoms. In addition, the sponsor submitted a reanalysis of study 1003A, which had been previously-submitted in the original NDA. Study 1003B did adequately support efficacy of the lowest dose, 0.0375 mg/day, while the larger study, 1003A, did not support efficacy of the lowest dose by the end of Cycle 1. Therefore, this product was approved with the following statement "Some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy."

Protocol 036 was designed to support the 0.0375 mg/day dose as the lowest effective dose in the treatment of moderate to severe vasomotor symptoms

Related Review: Statistical Review dated:

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3. Material Reviewed: Volumes 1-26

4. Chemistry/Manufacturing Controls: See Chemist approved review

5. Pharmacology/Toxicology: See Pharmacologist approved review

6. Clinical Background:

Estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. During the reproductive years the main source of estrogens is the dominant follicle and the corpus luteum it forms after ovulation. The principle estrogen produced is estradiol. By direct action, estrogen causes growth and development of the vagina, uterus, and fallopian tubes. In concert with prolactin, progesterone and other hormones, estrogens stimulate growth and development of the breast through ductal growth, stromal development and accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and the pigmentation of the nipples and genitals.

Loss of ovarian estradiol secretion after menopause can result in inability of thermoregulation causing hot flashes, associated with sleep disturbance and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopause women.

Transdermal administration of estrogen produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates and requires smaller doses than does oral therapy. Because estradiol has a short half-life (1 hour), transdermal administration of estradiol allows a rapid decline in blood levels after systems are removed, e.g. in a cycling regimen.

#### 6.1 Relevant human experience

Vivelle was originally sponsored by Noven Pharmaceuticals. Two clinical studies, 1003A and 1003B were submitted to support the efficacy of Vivelle. Noven committed to perform a Phase 4 study on March 4, 1994, after review of the lowest dose did not adequately support efficacy. Noven Pharmaceuticals received an approval letter from FDA October 28, 1994. Noven transferred the manufacturing and distribution of Vivelle to Ciba Pharmaceutical on December 9, 1994. Ciba and Sandoz Pharmaceutical combined to become Novartis Pharmaceutical in December 1996.

#### 7 Description of Clinical Data Sources

The sponsor conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the lowest dose (0.0375 mg/day) of Vivelle®. The start date for this study was July 9, 1996 and the completion date was July 29, 1997. Approximately 259 patients were randomized into this study.

#### 8 Clinical Study

##### Study 036

##### 8.1.1 Objective/rationale

The primary objective of this study was to confirm the efficacy of the lowest approved dose (0.0375 mg/day) of Vivelle®, compared to placebo, for the treatment of moderate to severe vasomotor symptoms. Secondly, the safety and tolerability of Vivelle was compared to placebo.

##### 8.1.2 Design

This was a randomized, double-blind, parallel group, 12-week, multicenter trial comparing Vivelle 0.0375 mg/day to placebo for the treatment of moderate to severe postmenopausal hot flushes.

##### 8.1.3 Source and number

Approximately 250 patients (125 patients per treatment group) were enrolled in this study in order to obtain a total of 228 evaluable patients per treatment group. Patients were recruited from the investigator's practices, physician referrals, and radio/newspaper advertisements.

## **Inclusion Criteria**

- Healthy, postmenopausal, female out-patients with or without an intact uterus requiring treatment for postmenopausal vasomotor symptoms;
- Age:  $\geq 35$  years (no upper limit);
- 12 months after last spontaneous menstrual bleeding (no specific requirement for  $E_2$ /FSH levels); or  
6 to < 12 months of amenorrhea with serum  $E_2$  value < 20 pg/mL and FSH value  $\geq 40$  mIU/mL; or  
6 weeks after bilateral oophorectomy (no specific requirement for  $E_2$ /FSH levels).  
Patients hysterectomized (without bilateral oophorectomy) prior to onset of menopause are acceptable if  $E_2$  value < 20 pg/mL and FSH  $\geq 40$  mIU/mL.
- A minimum of 7 hot flushes per 24 hours or 60 hot flushes per week.

## **And**

Overall severity rating of moderate to severe during at least 10 days of the two weeks run-in period.

Patient's diary must have records of the number and overall severity of hot flushes for at least 10 days during the two-week run-in period.

- Co-operative and freely consenting.

## **Exclusion Criteria**

### **Physiological states, previous and/or concomitant medical conditions**

- History of allergy to topical products containing any of the constituents of the patches.
- Undiagnosed vaginal bleeding within the past 6 months.
- Pap smear (performed with the last 6 months) showing dysplasia or malignancy.
- Mammogram (performed with the last 6 months) suggestive of malignancy.
- Endometrial thickness > 5 mm as assessed by transvaginal ultrasonography.
- History of or presence of endometrial hyperplasia.
- Presence of endometrial polyps and/or clinically significant leiomyomas of the uterus (uterus  $\geq 6$  weeks gestation size).
- History of or presence of carcinoma of endometrium, cervix, breast or ovary.
- Presence of malignancy of any other kind or history of such a malignancy during the past 5 years (except for localized basal skin cancer which has been successfully treated).
- Uncontrolled hypertension (i.e., repeated diastolic blood pressure values of > 95 mm Hg).
- Active thrombophlebitis or thromboembolic disease.
- History of myocardial infarction within the last 12 months.
- Generalized active skin disease likely to affect patch tolerability (e.g., eczema, psoriasis).

- Known severe chronic diseases (metabolic, endocrine, hepatic, cardiovascular, renal, etc.).
- Uncontrolled thyroid. In the case of thyroid hormone replacement, the patient must be clinically euthyroid and on a stable dose of thyroid hormone for at least 3 months.
- History of alcohol, drug abuse within the last 5 years.
- History of noncompliance to medical regimens and patients who are considered potentially unreliable.
- Any significant or laboratory abnormality that might, in the opinion of the investigator, compromise patient's safety, interfere with the evaluations, or preclude completion of the trial.

#### **Previous treatments**

- Previous estrogen or progestin treatment:

By injection/implants in the previous 6 months (before initiation of the run-in period)  
or oral route in the previous 8 weeks (before initiation of the run-in period)  
By transdermal or vaginal route in a the previous 4 weeks (before initiation of the run-in period)

- Any investigational drugs within the past 30 days prior to visit 1.

#### **Concomitant treatments**

- Drugs mentioned under previous treatments;
- Other drugs used for the treatment of climacteric symptoms (including antidepressants).
- $\alpha$  or  $\beta$ - blocking compound (including clonidine).
- Ergot or ergot derivatives.

Comment: Inclusion and Exclusion criteria are consistent with other estrogen replacement therapy protocols and are acceptable.

#### **Study Procedures**

Screening Visits 1 and 2 were used to assign a temporary, sequential screening number beginning with 901. Screening visit 1 was the initial visit and occurred -5 to -3 weeks prior to randomization. Patients signed an informed consent, and underwent a medical history, physical and gynecological examination, verification of a mammography and Pap test within the past 6 months, a transvaginal ultrasound, an endometrial biopsy, appropriate laboratory and safety tests, and serum E<sub>2</sub> and FSH levels. At the drug free run-in period of two weeks, patients were dispensed a diary card with instructions, and were told to record adverse experiences and concomitant medication while on non-drug therapy; additionally, all inclusion/exclusion criteria were checked and an interim physical examination including vital signs was provided.

At Visit 3 patients who met all admission criteria were randomized to one of the two treatments using the computer generated randomization schedule prepared by Novartis. The block size was not revealed. Patients were not stratified *a priori*.

Trial medication for each patient consisted of one of the following transdermal systems, Vivelle™0.0375 mg/day (11 cm<sup>2</sup>) or a matching placebo (11 cm<sup>2</sup>). The patients applied the test systems twice a week (on the same day of the week e.g., Monday and Thursday of each week), to a clean dry, unbroken area of the skin on the buttock that was not oily, damaged, or irritated. The waistline was to be avoided since tight clothing could rub off the system. The system was to be applied immediately after opening the pouch and removing the protective liner. If a system fell off, either the same system was reapplied or a new system was to be applied.

#### 8.1.4 Analysis

The sample size for this trial was based on the experience with trials previously conducted with this design. It was expected that the standard deviation of the number of hot flushes per day during Cycle 1 of the trial was 4.8 flushes per day, and the standard deviation of the severity of hot flushes was to be 1.39. In order to detect a mean difference of 0.52 in overall severity of hot flushes per day during Cycle 1 between placebo and Vivelle™0.0375 mg/day treatment groups with a significance level of 0.05 (two-sided) and power of 80%; a total of 114 evaluable patients per treatment group was required. This sample size was also sufficient to detect a mean difference of 2.0 in the total number of hot flushes per day. To allow for 10% of the patients not being considered acceptable for the analysis of the primary efficacy variable, a total of 250 patients (125 patients per treatment group) was randomized.

Comment: This statistical plan is sound and consisted with other clinical trials for ERT. It is powered to detect the effectiveness of the lowest dose of Vivelle.

### 8.1.5 Results

There were 259 patients randomized into the double blind treatment phase. The following table shows the disposition of patients by treatment groups:

Table 1

Distribution of patients by treatment groups (all randomized patients)

Number of Patients	Vivelle 0.0375 mg/day	Placebo	Total
Randomized	130	129	259
Treated (at least one application)	130	127 <sup>1</sup>	257
Completed	128	118	246
Discontinued prematurely <sup>2</sup>			
Total	2	11	13
For adverse experience	1	3	4
For unsatisfactory therapeutic effect	0	2	2
For any reason	1	6	7
Efficacy analyses			
Acceptable patients	125	117	242
Intent-to-Treat	130	127	257
In safety analyses			
Adverse experience evaluation	130	127	257
Safety Laboratory Evaluation	129	128	256

1 Two patients in the placebo group (M0465U/220 and M0458D/380) did not provide any post-baseline data and are, therefore, lost to follow-up. These two patients were excluded from both the safety and efficacy analyses.

2 Overall, 13 (5%) discontinued from the study prematurely. Of this total, 3 (1 in the 0.0375 mg group and 2 in the placebo group) were lost to follow-up. The 7 patients in the "for any reason group" appeared to have valid reasons for discontinuation.

Also note in table 1 a total of 15 patients (5 randomized to the Vivelle treatment group and 10 randomized to placebo treatment group) were excluded from the sponsor's acceptable patients in the primary efficacy variable.

Of the 15 patients not acceptable in the sponsor's analyses, 10 patients (3 Vivelle, 7 placebo) did not meet the inclusion requirement of overall severity rating of hot flushes to be moderate to severe during at least 10 days of the 2 week run-in period. In addition, 4 patients (2 Vivelle, 2 placebo) with less than 10 days of diary data during the last 2 weeks of cycle 1, and 1 placebo-treated patient who took estrogen (Estrace) on Days 14 to 16 of Cycle 1 were excluded from the acceptable patients analyses.

## **Under other administrative issues**

**Review of patient diary data revealed inconsistent reporting of the number of hot flushes and overall severity of hot flushes as follows:**

- **Patients reported the number of hot flushes during the day and during the night as zero, and failed to complete the rating of overall severity. The overall severity was assumed to be "none" in these cases for analysis purposes.**
- **Patients reported  $\geq 1$  flushes during the day and/or night and the overall rating of severity to be "none" (0). The data were analyzed without any modifications.**
- **Patients failed to report the number of hot flushes during the day and/or night; however the overall rating severity was reported as mild, moderate, or severe. The number of hot flushes was treated as missing data in these cases.**

**The majority of patients in this study took some type of concomitant medications during treatment. A review of the data showed that 81.5% of Vivelle treated patients and 89% of placebo-treated patients reported use of at least one concomitant medication or non-drug therapy during the trial. In most cases this included the use of analgesics, nonsteroidal anti-inflammatory drugs, antacids, antibiotics, antihistamines, antihypertensive, anxiolytics and nutrient supplements for the concomitant ailments or Prophylaxis. None of these were considered to have significant impact on the efficacy and/or safety assessments of Vivelle 0.0375 mg/day in this trial except as follows: A total of 8 patients took protocol-excluded medications (estrogen (2), antidepressants (3), and beta-blocker (3)).**

**Comment: Concomitant medications are consistent with other ERT studies. Daily diary data collection appears less than optimally desirable.**

**The sponsor presented baseline demographic information for all patients in table 7.1.1. Due to the size of this table, information will be summarized. The mean age was approximately 50.4 for both treatment groups. Ethnic origin in this study revealed 216 (83.4%) of the patients were White, 33 (12.74%) were Afro-American, and 10 (3.86%) were "Other." The treatment groups were comparable with a mean weight of 160.8 lbs. Menopausal status criteria included the following: > 12 months of amenorrhea 53 (20.26%), 6-12 months of amenorrhea 7 (2.70%), hysterectomized patients 49 (18.92%), post bilateral oophorectomy 149 (57.53%), and missing data, 1 (0.39%). In regard to smoking status, 63 (24.32%) were smokers and 196 (75.68%) were non-smokers. Mean baseline number of hot flushes were 11.41 in the Vivelle group and 11.59 in the placebo group; mean baseline severity of hot flushes (0-4 point scale) was 2.53 in the Vivelle group and 2.55 in the placebo group.**

## **Efficacy**

**The ITT population included all patients randomized in the study who applied at least one patch. One patient in the placebo group, #290 was excluded because she had only 3 days of diary data during the last two weeks of cycle 1. Therefore, the total ITT population is 256. In the sponsor's acceptable patient population, there are 125 patients in the Vivelle group, and 117 in the placebo population for a total of 242 patients. The sponsor did not perform an ITT analysis of cycle 1 in the submitted database.**

In a teleconference on November 2, 1999, a query was made to the sponsor regarding data for the ITT population for cycle 1. The sponsor's statistician provided information to FDA's statistician that allowed construction of an ITT population for cycle 1. Comparability of data results is the primary reason for comparing the ITT and the acceptable patient populations.

**Table 1**  
**Analysis Results for Change from Baseline in Mean Number**  
**Of Hot flushes per 24 hours in the last two weeks of Cycle 1**  
**ITT Population**

Cycle		Vivelle 0.0375mg/day		Placebo		Vivelle-Placebo	
		N	Mean(SD)	N	Mean(SD)	Difference	P-Value
1	Baseline	130	11.9(5.4)	126	11.7(5.5)		
	Post-treatment	130	4.0(4.2)	126	6.8(5.6)		
	Difference	130	-7.9(5.6)	126	-4.9(4.7)	-3.0	<0.001*

\* Significance is assessed when  $p < 0.05$  (two-sided)

Note there is a difference of 3 hot flushes per day in the ITT population which is statistically significant at the  $p < 0.001$  (two-sided).

**Table 2**  
**Analysis Results for Change from Baseline in Mean Number**  
**Of Hot flushes per 24 hours in the last two weeks of Cycle 1**  
**(All Acceptable Patients)**

Cycle		Vivelle 0.0375mg/day		Placebo		Vivelle-Placebo	
		N	Mean(SD)	N	Mean(SD)	Difference	P-Value
1	Baseline	125	11.69(5.2)	117	11.4(4.8)		
	Post-treatment	125	4.1(4.3)	117	7.1(5.7)		
	Difference	125	-7.41(0.37)	117	-4.27(0.39)	-3.14	<0.001*

\* Significance is assessed when  $p < 0.05$  (two-sided)

Although there is a difference of 5 patients in the Vivelle group and 9 in the placebo group compared to the ITT patient population, the difference in relief of symptoms is .14 between the ITT population and the acceptable population, with the same two-sided  $p < 0.001$ .

Comment: Review of the sponsor's ITT and acceptable patient populations did not show any significant difference. The above data supports the efficacy of Vivelle 0.0375 in the first 4 weeks of treatment.

The sponsor's main secondary efficacy variable was the analysis of change from baseline in the mean number of hot flushes per 24 hours for cycles 2 and 3. The following table shows those results:

**Table 3**  
**Analysis for Change from Baseline in Mean Number of Hot Flushes per 24 hours for Cycles 2 and 3(ITT patients)**

Cycle		Vivelle 0.0375mg/day		Placebo		Vivelle-Placebo	
		N	Mean(SD)	N	Mean(SD)	Difference	P-Value
2	Baseline	125	11.5 (5.2)	120	11.3 (4.8)		
	Post-treatment	128	2.9 (4.0)	120	5.9 (5.2)		
	Difference	128	-8.60(0.35)	120	-5.39(0.37)	-3.21	<0.001*
3	Baseline	124	11.5(5.2)	117	11.3(4.8)		
	Post-treatment	124	2.3(3.6)	117	5.6(4.9)		
	Difference	124	-9.24	117	-5.65(0.37)	-3.59	<0.001*

\* Significance is assessed when  $p < 0.05$  (two-sided)

Note that Vivelle is statistically better at cycles 2 and 3 in this analysis with differences -3.31 and -3.59 at the end of cycles 2 and 3. This supports sponsor's previous study showing efficacy after 1 cycle, but not in the first cycle.

**Table 4**  
**Analysis results for change from Baseline in Mean Overall Severity of Hot Flushes Cycles 2 and 3(ITT patients)**

Cycle		Vivelle 0.0375mg/day		Placebo		Vivelle-Placebo	
		N	Mean(SD)	N	Mean(SD)	Difference	P-Value
2	Baseline	129	2.5 (0.4)	120	2.6(0.4)		
	Post-treatment	129	1.0	120	1.7(0.8)		
	Difference	129	-1.55(0.07)	120	-0.83(0.08)	-0.71	<0.001*
3	Baseline	128	2.5(0.4)	118	2.5(0.4)		
	Post-treatment	128	0.8(0.9)	118	1.6(0.9)		
	Difference	128	-1.77(0.08)	118	-0.92(0.08)	-0.85	<0.001*

Note that Vivelle is statistically significantly better in cycles 2 and 3 in relieving the overall severity of hot flushes. As in the frequency analysis during cycles 2 and 3, there is a widening trend toward greater relief of symptoms when compared to placebo. This supports data seen in the original NDA.

The sponsor conducted the patient's global evaluation of treatment effectiveness at the end of Cycles 1, 2 and 3 and the patient's last global evaluation. Patients in the Vivelle treatment group tended to evaluate their condition as much improved or very much improved at the end of every trial cycle. Patient in the placebo treatment group had a tendency to assess their condition as minimally improved or slightly above minimally improved. The Wilcoxon rank sum test for each of the three cycles and for the last evaluation was significantly lower for the Vivelle 0.0375 treatment group than placebo ( $p < 0.001$ ).

## Safety

Descriptive terms used by the investigator to report AEs were converted into preferred terminology based on the International Medical Nomenclature (IMN) Dictionary (as defined by the World Health Organization and modified by Novartis). Preferred terminology is used in all AE summary tables; investigator terms are used in the by-patient data listings.

All patients treated with at least one application of trial drug (Vivelle130, placebo 127) were included in the safety analyses. The sponsor's table 9.1.1 shows the number and percentage of patients reporting adverse experiences by AE category and treatment group.

**Table 5**  
Number and percentage of patients reporting adverse experiences  
By AE category and treatment group (all ITT patients)

	Vivelle 0.0375mg/day (n=130)	Placebo (n=127)
Reported at least 1 AE	90 (69.2%)	79 (62.2%)
Reported at least 1 drug-related AE	42 (32.3%)	19 (15.0%)
Reported at least 1 serious AE	2 (1.5%)	0
Discontinued due to an AE	1 (0.76%)	3 (2.36%)

Note 4 patients discontinued due to adverse events in this trial and 2 patients reported at least 1 serious AE.

One or more AEs, whether or not drug related, were reported by 69.2% and 62.2% of Vivelle and placebo-treated patients respectively.

The sponsor's table 9.1.2 reported treatment emergent adverse events of  $\geq 1\%$  of all patients, whether or not trial drug related. The AEs were grouped by body system. It was noted that body system totals were not necessarily the sum of the individual study events since a patient could report two or more different events in the same body system. Table 9.1.2 will now be summarized in a descriptive fashion due to the size of this table. Only AEs which are  $\geq 5\%$  will be discussed. The most frequent AEs reported at least once were viral infection (Vivelle 10%, placebo 13.4%), breast pain (Vivelle 10.0%, placebo 0.8%), sinusitis (Vivelle 7.7%, placebo 8.7%), headache (Vivelle 6.2%, placebo 7.1%), insomnia (Vivelle 2.3%, placebo 7.1%), genital disorder, i.e., vaginal yeast infection (Vivelle 6.2%, placebo 1.6%), and upper respiratory tract infection (Vivelle 6.9%, placebo 4.7%).

Comment: all reported AEs are consistent with those seen in other ERT studies. Breast pain was the most frequently reported drug related AE, this is not unusual and is dose responsive. Since the lowest dose of Vivelle was studied, overall AEs are lower than those seen at higher dosages. Of note, application site reaction was reported for both treatment groups equally (3.1%).

Vaginal spotting and/or bleeding was reported by 12 of 34 (35.3%) nonhysterectomized Vivelle-treated patients and 5 of 25 nonhysterectomized placebo-treated patients.

The effect of Vivelle on the endometrium was evaluated by both transvaginal ultrasound (TVS) and by endometrial biopsy. In the ITT Vivelle treatment group, 33 patients had a visit 1 and visit 6 and 25 placebo patients had a visit 1 and 6. One Vivelle-treated patient and one placebo-treated patient did not have a post treatment ultrasonography performed and were excluded from the summary statistics. The mean endometrial thickness in the Vivelle group increased from 3.1 mm at Visit 1 to 5.8 mm at visit 6. In the placebo group the mean endometrial thickness increased from 3.2 mm at visit 1 to 3.8 mm at visit 6.

Review of the sponsor's table 9.5.6 showed a total of 22 of 34 (64.7%) nonhysterectomized Vivelle treated patients and 9 of 25 (36%) nonhysterectomized placebo-treated patients had endometrial thickness of > 4 mm following the trial treatment. Post treatment diagnosis of these 22 patients showed 3 patients to have an atrophic endometrium, 7 weakly-proliferative, 8 proliferative, and two to have simple hyperplasia (patients (M0468G/346, M0469K/357). In the placebo group biopsy results were 5 atrophic endometrium, 1 weakly proliferative, 3 proliferative and 0 hyperplasia.

**Comment:** Two simple hyperplasias in three months of treatment is surprising, but continues a trend observed with other transdermal products whereby lower dosages of transdermal ERT appear to deliver a greater amount of estrogen to the endometrium than lower dosages of oral estrogens thereby producing higher hyperplasia rates than seen with oral estrogens. Of interest would be the incidence of endometrial hyperplasia produced over a 12-month period in products considered low dose such as Vivelle 0.0375 mg/day and Vivelle 0.050mg/day compared to conjugated estrogens at 0.625.

Hematology, serum chemistry, and urinalysis testing were performed prior to trial treatment at Visit 1 (baseline), and at the end of trial treatment Cycle 3, Visit 6. Laboratory abnormalities considered by the investigator to be clinically significant and/or trial drug-related that were not present at baseline or worsened after trial treatment was reported in 8 patients (Vivelle 7, placebo 1). These laboratory abnormalities included elevated serum triglycerides (Vivelle 5, placebo 1), fasting glucose (Vivelle 1, placebo 1), alkaline phosphatase (Vivelle 1, placebo 1), SGOT (Vivelle 1) and SGPT (Vivelle 1). The elevation of serum triglyceride was considered trial drug-related in 3 Vivelle-treated patients; none of the other abnormalities were considered trial drug-related by the investigator.

#### **8.1.5.2 Reviewer's Comments/Conclusions of study results**

In this randomized, placebo-controlled study of twelve weeks duration, the 0.0375-mg Vivelle patch was statistically significantly better than placebo in the reduction of the frequency and severity of VMS. Efficacy was noted by the fourth week and was maintained throughout 12 weeks of treatment. Safety is comparable to other estrogen transdermal patches and in this study the usual AEs were seen at lesser rates than would be seen at higher dosages. Application sites reactions were reported in 3.1% of placebo and Vivelle patches.

**9 Overview of Efficacy**

The sponsor submitted a randomized, placebo-controlled study of 12 weeks duration in 259 patients at 12 centers in the US. A statistically significant reduction was shown for both the frequency and severity of VMS by the fourth week of treatment and continued for the remaining 8 weeks of the study. This study supports data seen in the original NDA, study 1003B, but not seen in study 1003A.

**10 Overview of Safety**

The sponsor included 257 patients in their summary of safety. There were no deaths in this trial. Two significant/potentially significant adverse events in this trial were related to a diagnosis of endometrial hyperplasia. It appears that Vivelle 0.0375 mg/day when unopposed by a progestin, may have a significant stimulatory effect upon the endometrium. This stimulatory effect may be even more pronounced at higher dosages, whether a progestin is given or not.

Based on laboratory data available in this study, an elevated triglyceride level was the only AE directly attributable to drug-related treatment.

**11 Labeling Review**

Labeling is reviewed from sponsor's submission of September 20, 1999. Previous drafts by the sponsor label were submitted on June 18, 1999 and on April 30, 1999. The draft label of September 20, 1999 will now be reviewed:

**Under Labeling for Health Care Providers:**



se

**Under Clinical Pharmacology:**



**Pharmacokinetics:**



**12 Conclusions**

The sponsor has demonstrated in protocol 36 that the 0.0375-mg/day dosage is effective and safe beginning at week 4 and continuing through weeks 8 and 12 of treatment.

**13 Recommendation**

Approval is recommended. The revised label should state that the starting dosage of Vivelle is 0.0375 mg/day and that decisions to increase dosage should not be made until after the first month of therapy.

*ISI*  
Phill H. Price, M.D.  
November 30, 1999 and  
December 14, 1999

*concern*

*ISI*

*12/27/99*

NDA 20-323/S-021

Vivelle® (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day

Novartis Pharmaceutical Corporation

**Safety Update Review**

In the sponsor's January 24, 2000, submission, the sponsor stated they have no new information to provide because the supplement was based on a single study (Protocol 36) and an Integrated Summary of Efficacy. No additional clinical studies in humans are ongoing since the filing of the supplemental NDA. Therefore, there are no additional adverse events of human experience to report in a safety update. No safety update memorandum will be prepared by the Medical Officer.

— /S/ —  
— *Acorn* —  
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/S/ 0 1 2/16/00