CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-538 Suppl. 014 and 015
Drug:	Vivelle-Dot (Estradiol Transdermal System) (0.025, 0.0375, 0.05, 0.075, and 0.10 mg/day)
Sponsor:	Novartis
Date of Submission:	1/18/01 and 1/22/01
Type of Submission:	Labeling Changes
Reviewer:	Venkateswar R. Jarugula, Ph.D.

Executive Summary

Vivelle-Dot in doses of 0.0375, 0.05, 0.075, and 0.1 mg/day is currently approved under NDA 20-538. The approval of Vivelle-Dot on January 8, 1999 was based on its bioequivalence to the original approved formulation of larger sizes, Vivelle (NDA 20-323).

NDA 20-538/S014 was submitted on 1/18/01 to propose a labeling change for Vivelle-Dot (estradiol transdermal system) to incorporate the labeling changes that were approved on February 25, 2000 for Vivelle (NDA 20-323/S021). Supplement 015/NDA 20-538 was submitted subsequently on 1/22/01 incorporating further labeling changes for Vivelle-Dot to include osteoporosis indication and lower dose of 0.025 mg/day, again based on the bioequivalence between Vivelle-Dot and Vivelle. These two supplements have been evaluated together in this review.

Supplement 014

In this supplement, Sponsor revised the current labeling of Vivelle-Dot to remove the restrictive labeling language concerning the efficacy of 0.0375 mg dose. The restrictive language was removed from the labeling of Vivelle following the approval of NDA 20-323/S021 based on a clinical trial. Since Vivelle-Dot and Vivelle were shown to be bioequivalent, sponsor's proposal to remove the restrictive language concerning the efficacy of 0.0375 mg/Day dose in Vivelle-Dot label is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

Supplement 015

Supplement 015 seeks to include osteoporosis indication for Vivelle-Dot from 0.025 through 0.1 mg/day and requests for biowaiver for 0.025 mg/Day strength based on the following:

- Vivelle in doses 0.025 to 0.1 mg/day has been approved under NDA 21-167/NDA 20-323 (S023) for the indication of prevention of postmenopausal osteoporosis.

- Vivelle-Dot has been shown to be bioequivalent to Vivelle at the highest strength of 0.1 mg/day.

- Different doses of Vivelle-Dot are compositionally proportional as they are cut from the same laminate.

- In vitro dissolution profiles of all strengths of Vivelle-Dot are comparable (F2>50).

- Pharmacokinetics of Vivelle-Dot are dose proportional over the dose range of 0.025 to 0.1 mg/day.

- Vivelle-Dot is bioequivalent to Vivelle at 0.05 mg/day following multiple administration at steady-state.

Based on the above mentioned results, sponsor's proposal to include prevention of osteoporosis indication for the dose range of 0.025 to 0.1 mg/day of Vivelle-Dot and biowaiver for 0.025 mg/Day strength are acceptable.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) has reviewed the supplement No. 014 and 015 to NDA 20-538 and these supplements are acceptable. Labeling comments in Labeling section of the review should be communicated the sponsor as appropriate.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D. _____

FT signed by Ameeta Parekh, Ph.D. _____

cc: NDA 20538/S014/S015, HFD-580 (Price, Moore), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B.Murphy for Drug).

Clinical Pharmacology and Biopharmaceutics Summary

Dose Proportionality

An open-label, single dose, randomized, 4-treatment, 4-period crossover study was conducted to determine the dose proportionality of Vivelle-Dot (doses 0.025, 0.0375, 0.05, and 0.1 mg/day). Thirty two (32) postmenopausal, otherwise healthy women participated in the study with the following treatments:

Treatment A: One Vivelle-Dot 2.5 cm2 patch (0.025 mg/day)
Treatment B: One Vivelle-Dot 3.75 cm2 patch (0.0375 mg/day)
Treatment C: One Vivelle-Dot 5.0 cm2 patch (0.05 mg/day)
Treatment D: One Vivelle-Dot 10.0 cm2 patch (0.1 mg/day)

A minimum of 7-day washout period from the time the systems were removed was allowed between the treatments. Each subject applied the patch for 3.5 days one side of the abdomen below the waistline. The 2.5 cm^2 and 10 cm^2 patches were of circle shape and the other two patches (3.75 cm^2 and 5.0 cm^2) were of rounded rectangle shape (commercial shape). Although the shapes are different, all the patches were of same surface area and were cut from the same laminate using the final market formulation.

Table 1. Mean (SD) estradiol pharmacokinetic parameters (base-line corrected)

Parameter	**0.025 mg/Day**	**0.0375 mg/day**	**0.05 mg/day**	**0.1 mg/day**
Cmax (pg/ml)	24.0 (9.8)	34.8 (12.2)	50.1 (18.5)	96.0 (33.9)
Tmax (h)	38.0 (19.3)	32.5 (13.0)	28.5 (16.8)	33.7 (16.1)
AUC0-84 (pg.h/ml)	1327 (496)	1893 (665)	2525 (969)	5333 (1947)
AUC0-∞ (pg.h/ml)	1403 (520)	2007 (687)	2662 (1023)	5628 (2003)
T1/2 (h)	3.8 (1.3)	4.1 (1.4)	4.1 (1.2)	5.1 (1.7)

Table 2. Mean (SD) estrone pharmacokinetic parameters (base-line corrected)

Parameter	**0.025 mg/Day**	**0.0375 mg/day**	**0.05 mg/day**	**0.1 mg/day**
Cmax (pg/ml)	10.5 (5.8)	15.2 (6.5)	21.8 (10.1)	41.0 (16.7)
Tmax (h)	54.9 (19.6)	54.8 (20.2)	52.8 (20.8)	58.8 (15.2)
AUC0-84 (pg.h/ml)	559 (368)	852 (426)	1194 (559)	2380 (1072)
AUC0-96 (pg.h/ml)	587 (402)	872 (491)	1275 (661)	2660 (1206)

The systemic exposure of estradiol and estrone increased in linear and dose proportional manner with increasing dose from 0.025 mg/day through 0.1 mg/day.
The market formulation is of rounded rectangle. It is not clear why sponsor used a slightly different shape (circle) patches for 0.025 and 0.1 mg/day doses. However, this might not affect the assessment of dose proportionality of Vivelle-Dot as the difference in shape is not significant and the different sizes and shapes are cut from the same laminate of market formulation.

Multiple Dose Bioequivalence Study

A multiple dose steady state bioequivalence study was conducted in thirty-two postmenopausal healthy women who were administered the following transdermal systems in a randomized and crossover fashion:

Treatment A: One 5 cm^2 Vivelle-Dot (0.05 mg/day) ETS applied every 84 hours for 4 dosing intervals

Treatment B: One 14.5 cm^2 Vivelle (0.05 mg/day) ETS applied every 84 hours for 4 dosing intervals

Table 3. Mean baseline corrected pharmacokinetic parameters of estradiol and bioequivalence

Parameter	Vivelle-Dot (5 cm2)	Vivelle 14.5 cm2)	90% CI
Cmax (pg/ml)	51.7 (29.0)	48.5 (21.3)	88.6 – 118.9
Tmax (h)	30.7 (15.6)	22.0(13.5)	
AUC0-t	2672 (1440)	2539 (1268)	88.9 – 124.96
AUC0-96	2793 (1524)	2656 (1324)	
Cmin	23.1 (15.0)	25.3 (13.6)	

Parameter	Vivelle-Dot (5 cm2)	Vivelle 14.5 cm2)	90% CI
Cmax (pg/ml)	21.3 (12.8)	20.8 (9.7)	73.4 – 114.9
Tmax (h)	42.4 (24.8)	35.4 (21.3)	
AUC0-t	1273 (926)	1208 (586)	83.2 – 111.4
AUC0-96	1280 (1054)	1204 (680)	
Cmin	12.9 (12.9)	11.8 (8.0)	

Vivelle-Dot was bioequivalent to Vivelle at 0.5 mg/day dose following multiple dose application based on both estradiol and estrone levels except for Cmax of estrone which is slightly out of 80 to 125% range.

Adhesion

Adhesion data for Vivelle-Dot was collected in two bioavailability studies (N09-004, N09-005) and one adhesion study (N09-008). In all three studies, the adhesion performance of Vivelle-Dot was evaluated (by the investigator or his study staff) for each patch applied at the end of the 84 hour wear period. The pooled adhesion data from the three studies is summarized in the following table.

Table 4. Adhesion scores for Vivelle-Dot (pooled data from Studies N09-004, N09-005, N09-008)

Treatment	0.025 mg@	0.0375 mg	0.05 mg	0.1 mg@	all doses
No. of subjects	31	32	163	31	164
No. of Observations	31	33	376	31	471
Adhesion score#					
0	30 (96.8%)	25 (75.8%)	320 (85.1%)	24 (77.4%)	399 (84.7%)
1	1 (3.2%)	8 (24.2%)	41 (10.9%)	5 (16.1%)	55 (11.7%)
2	0	0	1 (0.3%)	1 (3.2%)	2 (0.4%)
3	0	0	0	0	0
4	0	0	14* (3.7%)	1(2.3%)	15 (3.18%)

@ 0.025 mg and 0.1 mg strengths were of circle shape.
*included 3 subjects who used tape after the systems came off.

# Adhesion scores:		
	0	patch adhered >90% ("completely on")
	1	patch adhered 75-90% ('edges lifting off' or "center raised")
	2	Patch adhered 50-74% ("half off")
	3	Patch adhered <50% ("just hanging on")
	4	Patch not present on skin or if reapplied by subject

Based on the combined adhesion data shown above, about 85% of Vivelle-Dot transdermal systems adhered completely over the 84 hour (3.5 day) wear period, while 12% had edges come off and 0.4% were 'half off'. About 3% of the transdermal systems detached completely during the 84 hour wear period and were reapplied. Or replaced. Approximately 80% of the systems evaluated in these studies were of 0.05 mg/Day strength of Vivelle-Dot.

Labeling

Based on the above results, the adhesion section of the proposed labeling in supplement 015 should be modified as follows:

Based on combined data from three short-term clinical trials consisting of 471 observations, 85% of Vivelle-Dot ' ——————— adhered completely to the skin over the 3.5 day wear period. Three percent (3%) of the systems detached and were reapplied or replaced during the 3.5 day wear period. Approximately 80% of the transdermal systems evaluated in these studies were Vivelle-Dot™ 0.05 mg/day.

In Vitro Dissolution

In vitro release data for 0.025 mg/Day (2.5 cm^2) system and the four current marketed strengths Vivelle–Dot are provided in the submission.

Table 5. In vitro (%) release comparison

Size (cm^2)	2 h	4 h	6 h	F2
2.5	24	37	48	
3.75	25	39	50	84.9
5.0	27	39	49	81.2
7.5	32	48	55	52.6
10.0	31	44	54	58.5

Based on the release profiles and F2 comparisons, the release of 0.025 mg/Day is similar to that of other approved strengths.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Venkateswar Jarugula
11/7/01 10:17:04 AM
BIOPHARMACEUTICS

Ameeta Parekh
11/7/01 02:23:53 PM
BIOPHARMACEUTICS
I concur.

New Drug Application Filing Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA:	20-538/S015	**Priority Classification:**	
IND:		**Indication:**	Osteoporosis
Brand Name:	Vivelle-Dot	**Submission Date:**	01/22/01
Generic Name:	Estradiol transdermal system	**Route of Administration:**	Transdermal
Chemical Type:	Femalw sex steroidal hormone	**UFGD:**	11/23/01
Sponsor:	Novartis	**Review Division:**	HFD-870
Reviewer:	Venkat Jarugula, Ph.D.	**Medical Division:**	HFD-580
Team Leader:	Ameeta Parekh, Ph.D.		

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Study Synopses	X		
Labeling	X		
Bioavailability and Bioequivalence Studies:			
ADME Study –			
BA Studies – **Absolute BA** **Relative BA**			
BE Studies – **Population BE** **Individual BE**	X		
Food-Drug Interaction Study			
In Vitro-In Vivo Comparison (IVIVc) Studies			
Reference Bioanalytical and Analytical Methods	X		
Dissolution Profiles	X		
Studies Using Human Biomaterials			
Plasma Protein Binding Studies			
Metabolism Studies Using Hepatocytes, Microsomes, etc.			
Blood / Plasma Ratio			
Human Pharmacokinetics (PK) Studies:			
PK and Initial Safety and Tolerability in <u>Healthy</u> Volunteers – **Single Dose** **Multiple Dose**			
PK and Initial Safety and Tolerability in <u>Patient</u> Volunteers – **Single Dose** **Multiple Dose**			
Dose Proportionality – **Single Dose** **Multiple Dose**	X		
PK in Population Subsets to Evaluate Intrinsic Factor Effects – **Ethnicity** **Gender** **Pediatrics** **Geriatrics** **Renal Impairment** **Hepatic Impairment**			

PK in Population Subsets to Evaluate Extrinsic Factor Effects – In-Vivo Effects on Primary Drug In Vivo Effects of Primary Drug In-Vitro Drug Interaction			
Population PK Studies			
Summary of PK / PD Studies			
PK / PD Studies in Volunteers			
PK / PD Studies in Patients			
Individual Datasets for all PK and PK / PD Studies in Electronic Format			
Other:			
Genotype / Phenotype Studies			
Chronopharmacokinetics			
Literature – Number of Articles Sufficient			
Which Phase IV Studies Requested? 1. 2. 3.			

This Application (__X__ is; ____ is not) filable.

If not filable, discuss reason(s) why below:

Comments to be sent to Sponsor:

Venkat Jarugula, Ph.D.; FDA / CDER / OPS / OCPB / DPE-II

Ameeta Parekh Ph.D., Team Leader; FDA / CDER / OPS / OCPB / DPE-II

CC: NDA # (20-538/S015), HFD-580 (Price, Moore), HFD-850 (Lesko, Huang), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B.Murphy)

/s/

Venkateswar Jarugula
3/7/01 02:13:43 PM
BIOPHARMACEUTICS

Ameeta Parekh
3/13/01 11:05:22 AM
BIOPHARMACEUTICS
I concur