CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-167/N-000	**SUBMISSION DATE:**	**19-OCT-99**
BRAND NAME:	**Vivelle®**	
GENERIC NAME:	**Estradiol transdermal system**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novartis Pharmaceuticals Corp., East Hanover, NJ**	
TYPE OF SUBMISSION:	**Efficacy Supplement Code: 3S**	

SYNOPSIS:

This NDA submission seeks approval of a lower strength 0.025mg/day Vivelle transdermal system. This proposed system is proportional (active and inactive ingredients) to the approved higher strength systems (0.0375, 0.05, 0.075, and 0.1mg/day), uses the same release mechanism as the approved systems, and was used in a clinical trial for the proposed indication of prevention of postmenopausal osteoporosis. The sponsor has requested FDA to waive the requirement for the submission of evidence demonstrating bioavailability of the drug product. The waiver has been granted.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-167/N-000 submitted 19-OCT-99. The waiver for the requirement for the submission of evidence demonstrating bioavailability of the drug product is granted.

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(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Vivelle was approved under NDA 20-323 on 28-OCT-94 for the treatment of patients with estrogen deficiency syndrome, specifically: 1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause; 2) Treatment of vulval and vaginal atrophy; and 3) Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The Vivelle system should be replaced twice weekly and is available in the following formulations:

- 0.0375 mg/day - each 11.0 cm^2 system contains 3.28 mg of estradiol USP for nominal delivery of 0.0375 mg of estradiol per day.

- 0.05 mg/day - each 14.5 cm^2 system contains 4.33 mg of estradiol USP for nominal delivery of 0.05 mg of estradiol per day.
- 0.075 mg/day - each 22.0 cm^2 system contains 6.57 mg of estradiol USP for nominal delivery of 0.075 mg of estradiol per day.
- 0.1 mg/day - each 29.0 cm^2 system contains 8.66 mg of estradiol USP for nominal delivery of 0.1 mg of estradiol per day.

The Vivelle-Dot system, approved under NDA 20-538 on 31-JUL-96, is a reduced size system as compared to Vivelle. The Vivelle-Dot system has been shown to be bioequivalent to the Vivelle system.

By way of NDA 21-167/N-000 the sponsor seeks approval of a 0.025 mg/day system. This would be the recommended starting dose for prevention of postmenopausal osteoporosis; the dose can be adjusted as necessary. Clinical trial data have been submitted in the current NDA to support this indication.

The sponsor has submitted two skin tolerability and adhesion studies which are not reviewed in this document.

DRUG FORMULATION:

What are the formulations of the approved Vivelle systems?
How does the new lower strength 0.025mg/day system compare with the approved systems?

The formulations for the five systems are presented in the table below. The proposed 0.025 mg/day system is proportional in active and inactive ingredients to the next higher strength system. Indeed, all the systems are proportional. Also, the same release mechanism is used in the 0.025 mg/day system as in the approved systems.

DRUG PRODUCT COMPOSITION

ESTRADIOL TRANSDERMAL SYSTEM

Code No.	Ingredient	Trade Name	Function	Theoretical mg/cm2 *	Theoretical mg/1.35cm2 unit **	Theoretical mg/1[illegible] unit **	Theoretical mg/14.5cm2 unit **	Theoretical mg/23cm2 unit **	Theoretical mg/[illegible]cm2 unit **
	Adhesive Containing Estradiol								
N032	Estradiol USP			0.298	2.16	3.28	4.33	6.57	8.65
N195	Acrylic Adhesive								
N015	Polyisobutylene								
N001	Oleic Acid NF								
N014									
N004	Vinyl Acetate								
N010									
N019	Benzoate NF								
N007	1,3-Butylene Glycol								
N028	Mineral Oil USP								
N027	Dipropylene Glycol								
N031									
Carrier System									
	Backing								
PI 708W									
	Protective Liner								
F100006									

* Amounts reported on a dry basis.
** Quantities rounded to 3 significant figures
# Removed from product during [illegible] procedure.

DISCUSSION:

In a 17-FEB-99 FAX sent to the sponsor (Appendix 2), three requirements for waiving the bioavailability requirement were explained. The sponsor has met all three of these requirements and therefore the waiver is to be granted.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ 12-JUL-00

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 12-JUL-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 7/12/00

CC: NDA 21-167/N-000 (orig.,1 copy), HFD-510(Koch), HFD-870(Ahn, HuangS), HFD-850(Lesko) CDR.

DFS Code: AP

APPEARS THIS WAY
ON ORIGINAL

Appendix 1. Draft labeling

18 page(s) of revised draft labeling has been redacted from this portion of the review.

Appendix 2. Previous Communication