

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-538/S-015**

**CHEMISTRY REVIEW(S)**

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG  
PRODUCTS**

**REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS  
CHEMIST'S REVIEW #1**

1. NDA NUMBER: 20-538
2. NAME AND ADDRESS OF APPLICANT  
Novartis Pharmaceutical Corporation  
59 Route 10  
East Hanover, NJ 07936-1080
3. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED  
SE1-015 /1-22-01/1-23-01
4. NAME OF THE DRUG: Vivelle-Dot<sup>TM</sup> (estradiol transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: A new indication of Vivelle-Dot for the prevention of postmenopausal osteoporosis
7. AMENDMENTS/REPORTS/ DATE: SE1-015BC /7-17-01/10-1-01/10-16-01
8. PHARMACOLOGICAL CATEGORY  
Estrogen/HRT
9. HOW DISPENSED  
Prescription
10. RELATED IND/NDA/DMF/SUPPLEMENT  
None
11. DOSAGE FORM : Transdermal
12. POTENCY  
0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day
13. CHEMICAL NAME AND STRUCTURE  
 $C_{18}H_{24}O_2$   
MW = 272.4

*Estra-1,3,5(10)-triene-3,17 $\beta$ -diol*

6 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-1

**14. COMMENTS**

The 0.0375, 0.05, 0.075, and 0.1 mg/day strengths were approved earlier under supplement S-006 (approval date January 8, 1999). The sponsor submitted this application for approval of all four strengths (0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day) for the osteoporosis indication. There is no formulation change. The drug product is die cut to 3.75 Cm<sup>2</sup> from a common laminate to achieve the delivery rate of 0.025 mg/day. The sponsor also provided labeling of the 0.025 mg/day strength.

In the amendment, dated 7-17-01, the sponsor submitted a modified stability commitment. In the amendment dated 10-1-01, the sponsor provided the updated stability data, and incorporated the acceptance criteria for vinyl acetate. In the amendment, dated 10-16-01, the sponsor provided the EIC calculation in support of the categorical exclusion claim for Environmental Assessment.

**15. CONCLUSIONS AND RECOMMENDATIONS:** The supplement may be approved with respect to CMC.

Reviewed By: Amit K. Mitra, Ph.D, 10-14-01

R/D INIT. BY: Moo-Jhong Rhee, Ph.D

CC: A. K. MITRA/HFD-580  
M.J.RHEE/HFD-580  
D. Moore/HFD-580  
NDA 20-538

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/s/

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Amit K. Mitra  
10/18/01 03:44:09 PM  
CHEMIST

Moo-Jhong Rhee  
10/18/01 05:38:18 PM  
CHEMIST  
I concur