CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-655/S-008

Clinical Pharmacology and Biopharmaceutics Reviews

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Myong-Jin Kim, HFD 870			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 16/JAN/2002	IND No.: Serial No.:	NDA No. 20-655 S-008	DATE OF DOCUMENT 20/NOV/2001	
NAME OF DRUG **[Alora]**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: [Watson Pharma, Inc.]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

Reference is made to the approved NDA 20-655, Alora® (Estradiol Transdermal System). Reference is also made to the Clinical Pharmacology & Biopharmaceutics Review by Dr. Michael J. Fossler dated 23/OCT/98 (NDA 20-655/S-003, submission date 27/AUG/98).

In Dr. Fossler's review, Study "Comparison of the Wear Properties of Placebo TheraDerm Matrix Transdermal Delivery Systems (MTDS 18 cm^2) Manufactured with Different Levels of Adhesive" was evaluated to determine wear properties of estradiol transdermal system. The study was a single-blind, multi-center, multi-application comparison of test placebo systems (contains a cross-linker, acetyl acetonate, 0.10% w/w) with control product (aluminum acetyl acetonate, 0.39% w/w). Adhesion potentials of placebo transdermal systems that correspond to the 18 cm^2 sizes of Alora 0.05 mg/day were conducted in 408 healthy postmenopausal women. Each woman applied transdermal systems twice weekly on the lower quadrant of the abdomen for 4 weeks. The wear performance of the system was evaluated after 3.5 days and was repeated a total of 8 times. The primary variable was adhesion rate using the following scale:

0 = greater than 75 % of the system adhered to skin.

1 = ~ 75 % of the system adhered to skin.

2 = system is detached.

For statistical analysis, these scale scores were converted to a dichotomous variable where 0 = completely detached and 1 = partially or completely adhered. A total of 968 adhesion observations were conducted using acetyl acetonate 0.10 %. Transdermal systems had an approximate partial or complete adhesion rate of 97 %. The total detachment rate was approximately 3 %.

Labeling Recommendation:

Adhesion

" [redacted]
applied twice weekly for four weeks on the lower quadrant of the abdomen. It should be noted that lower abdomen, the upper quadrant of the buttocks or outer aspect of the hip are the approved sites of applications for Alora. Subjects were instructed not to do strenuous activities, take baths, use hot tubs or swim. [redacted] The total detachment rate was approximately 3 %. Adhesion potentials [redacted] 9 cm^2, 27 cm^2 and 36 cm^2 sizes [redacted] have not been studied."

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: HFD # [580]; TL: [Parekh]; DD: [Malinowski]	**Project Manager:** _____ **Date** _____

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

/s/

Myong-Jin Kim
1/17/02 08:52:18 AM
PHARMACOLOGIST

Ameeta Parekh
1/18/02 01:53:20 PM
BIOPHARMACEUTICS
I concur