CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-375/S-016

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Climara, estradiol, transdermal system, vasomotor symptoms
Reviewer Name: Krishan L. Raheja
Division Name: DRUDP
HFD#: 580
Review Completion Date: 6-22-2000

Review number: 001
IND/NDA number: NDA 20-375.SE-016
Serial number/date/type of submission: 6-2-2000/Efficacy supplement
Information to sponsor: Yes ( ) No ( )
Sponsor (or agent): Berlex Laboratories, Inc. Montville, NJ
Manufacturer for drug substance:

Drug product: Climara (estradiol transdermal system)

Relevant INDs/NDAs/DMFs: NDA 20-375

Drug Class: estrogens

Indication: treatment of vasomotor symptoms associated with menopause

Clinical formulation: 6.5 cm^2 transdermal system delivering 0.025 mg estradiol/day

Route of administration: transdermal

Proposed clinical protocol or Use: To be used for the treatment of vasomotor symptoms associated with menopause

Previous clinical experience: Climara (estradiol transdermal system) designed to deliver 0.05, 0.075 and 0.1 mg estradiol/day has been previously approved by the FDA for the treatment of vasomotor symptoms and osteoporosis associated with menopause.

Disclaimer -- use of sponsor's material

Introduction and drug history: 3M Pharmaceuticals received FDA approval in 1994 under NDA 20-375 for Climara 12.5 cm^2 and 25.0 cm^2 systems delivering 0.05 and 0.1 mg estradiol/day. In 1995 all rights to NDA 20-375 for Climara were transferred to Berlex Laboratories, Inc. In 1998, Berlex Laboratories, Inc. received approval of supplement S-009 to NDA 20-375 for the treatment of moderate to severe vasomotor symptoms associated with menopause for the 18.75 cm^2 system delivering 0.075 mg estradiol/day. In 1999, Berlex Laboratories, Inc. received FDA approval of supplement S-011 to NDA 20-375 which provided for the already 3 approved formulations plus a new fourth strength of 0.025 mg estradiol/day for delivery via a 6.5 cm^2 system for the prevention of postmenopausal osteoporosis.

Supplement S-011 did not provide for the indication of treatment of vasomotor symptoms associated with menopause, for the new fourth (lowest approved) patch strength.

The purpose of the present supplement is to modify the existing Climara labeling to provide for the indication of treatment of moderate to severe vasomotor symptoms associated menopause, for the lowest approved patch strength (6.5 cm^2 patch delivering 0.025 mg estradiol/day).

To support this indication, sponsor has conducted 2 clinical studies, one compared to placebo and second compared to oral conjugated estrogens.

Sponsor has stated that there are no additions or changes to the nonclinical pharmacology and toxicology information provided in approved NDA 20-375 for this product.

RECOMMENDATIONS: Based on extensive clinical experience with Climara for the treatment of moderate to severe vasomotor symptoms associated with menopause with patches of higher strength than the one proposed in the present submission, Pharmacology recommends approval of supplement 016 to NDA 20-375 to modify the existing Climara labeling as requested by the sponsor.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

(S)

cc: HFD-580/A.Jordan/K.Raheja/D. Spell-LeSane

(S) 6/27