CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-048

PHARMACOLOGY REVIEW

FEB 17 1999

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:
Reviewer Name: Alex Jordan
Division Name: DRUDP
HFD#580
Review Completion Date: 2/17/99

Review number: 001
IND/NDA number: NDA 21-048
Serial number/date/type of submission
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Wyeth-Ayerst
Manufacturer for drug substance: Wyeth-Ayerst?

Drug:

Code Name: estradiol
Generic Name: estradiol
Trade Name: 17B-Estradiol Transdermal System (E2 III TS)
Chemical Name:
CAS Registry Number:
Molecular Formula/ Molecular Weight:
Structure:

Relevant INDs/NDAs/DMFs:

Drug Class: estrogens

Indication: Estrogen replacement therapy (ERT) for treatment of moderate to severe vasomotor symptoms associated with menopause, vulvar and vaginal atrophy

Clinical formulation: The transdermal system consists of estradiol; polyvinylpyrrolidone (PVP) — also known as Povidone, USP; Aluminum acetylacetonate as a —— and —— which is the adhesive consisting of

Route of administration: Transdermal

Proposed clinical protocol or Use: Daily administration by patch for menopausal symptoms

Previous clinical experience: Yes

Disclaimer – use of sponsor's material

Introduction and drug history:

Studies reviewed within this submission:

Studies not reviewed within this submission:

TOXICOLOGY:

General Comments: Two studies are reviewed for this NDA

Study Title: 4-week dermal toxicity study with 17Bestradiol trandsermal patch in rabbits
Study No: GTR-30982
Amendment #, Vol #, and page #: Vol 1.005 pg 1
Conducting laboratory and location:
Date of study initiation: 1995
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods: Two gps received either placebo transdermal patches (15 females/gp) or test transdermal patches (2.93 mg estradiol/patch). There were 4 sites, each site received a new patch for 7 days for a total of 28 days. Sites were scored for irritation.
Dosing:

- species/strain: Female Hra: (NZW) SPF rabbits
- #/sex/group or time point: 15
- age:15 weeks
- weight: 2.254- 2.750 kg
- satellite groups used for toxicokinetics or recovery:
- dosage groups in administered units:
- route, form, volume, and infusion rate:

Drug, lot#, radiolabel, and % purity:
Formulation/vehicle:
Observations and times:

- Clinical signs:
- Body weights:
- Food consumption:
- Ophthalmoscopy:
- EKG:
- Hematology:
- Clinical chemistry:
- Urinalysis:
- Organ weights:
- Gross pathology:
- Organs weighed:
- Histopathology:
- Toxicokinetics:
- Other:

Results:

- Clinical signs:
- Body weights
- Food consumption
- Ophthalmoscopy
- Electrocardiography
- Hematology
- Clinical chemistry
- Urinalysis
- Organ Weights

- Gross pathology
- Histopathology
- Toxicokinetics

Key Study Findings: There were no unusual findings. There were estrogen induced changes in the uterus. Irritation scores were within the expected range of irritation.

Study Title: Dermal sensitization (Buehler method-modified) of the cygnus estradiol III TDS transdermal patch in guinea pigs (II)
Study No: X4F245G
Amendment #, Vol #, and page #: Vol 1.005 pg 397
Conducting laboratory and location: [redacted]
Date of study initiation: 1994
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods: Hair was clipped the day before dosing. Test material was applied on 13 mm diameter patch disks. The positive control (1-chloro-2, 4-dinitrobenzene) was applied in 0.2 ml using Hill Top Chambers. After application, the animals were wrapped in guaze, about 12 hrs after the first induction exposure, the animals were unwrapped, wiped with 70% alcohol. The dosing procedure was repeated 3 times/wk for 3 wks. Test material was applied to the same site for each exposure. For the positive controls, the site was moved when scores of 3 (edema or cracking of the skin) occurred. Scoring was done 24 hrs after the induction phase. Challenge Phase – 13 days after the third induction exposure, the animals were clipped at a previously unexposed site. The test materials were applied in thesame manner as in the induction phase, as 13 mm patch disks. Six hrs after the patch application, the animals were unwrapped and the sites wiped gently with 70% alcohol. 24 and 48 hrs after patch removal, the sites were scored.

After challenge, one treated animal had a score of 1 (slight confluent or moderate patchy erythema). When rechallenged, it had a score of +/- (slight patchy erythema). No other animal had a score of greater than +/-. The positive controls all had a severity score of 1 or greater.

The sponsor states that these results show that the patch is not a contact sensitizer.

Dosing:
- species/strain: Hartley albino guinea pigs
- #/sex/group or time point: 10 males; there were two treated gps using different batches of drug. The positive control gp had 5 animals and the placebo gp had 10.
- age: 4 wks or older
- weight: at least 250 g
- satellite groups used for toxicokinetics or recovery: No
- dosage groups in administered units:
- route, form, volume, and infusion rate: transdermal patch

Drug, lot#, radiolabel, and % purity:
Formulation/vehicle:
Key Study Findings: The test system is not a contact sensitizer.

Overall Toxicology Summary: Estradiol is an approved drug and presents no safety concern. The patch consists of polymers with a history of use in patches. Monomers present a theoretical risk but the risk is extremely small under real use conditions. In the finished system, the

unpolymerized HEA and GMA were below the limits of detection ([redacted]
respectively) and the levels of unpolymerized VA and EHA were detected at up to [redacted] and [redacted] respectively. These levels of monomers provide adequate margins of safety. Based on mutagenicity studies, the margin of safety for VA are 3 and 850 based on theoretical human exposure in skin and plasma, respectively, and 1,800,000 based on dose. This monomer presents the greatest safety risk of all the monomers.

There was minimal to moderate irritation with the patch in rabbits and there was contact sensitization in one of 20 animals in the guinea pig sensitization test.

Addendum list:

OVERALL SUMMARY AND EVALUATION:

Introduction:
Safety Evaluation: There is no problem with estradiol. The contents of the patch present no significant safety concerns.
Clinical Relevance of Safety Issues:
Other Clinically Relevant Issues:
Conclusions: The NDA is approvable from the standpoint of Pharmacology

Communication Review:
- Labeling Review (NDA): Follows estrogen labelling format
- Investigator's Brochure/Informed consent review (IND):

RECOMMENDATIONS: I recommend approval of NDA 21-048

Internal comments:
External Recommendations (to sponsor):
Draft letter Content for Sponsor:
Future development or NDA issues:
Reviewer signature/team leader signature [Concurrence/Non-concurrence]

Alex Jordan 2/17/99

cc: list HFD-580; AJordan/DMoore
Draft date (# of drafts):
Memorandum of Non-concurrence (if appropriate, attached):
Addendum to review (if necessary):
Appendix/attachments: