CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-258

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-258
Review number: 1
Serial number/date/type of submission: 001; 6/29/00; original NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Berlex
Manufacturer for drug substance:

Reviewer name: Alex Jordan
Division name: DRUDP
HFD #: 580
Review completion date: 6/5/01

Drug:

Trade name: Estradiol/Levonorgestrel Transdermal System
Generic name (list alphabetically):
Code name:
Chemical name:
CAS registry number:
Mole file number:
Molecular formula/molecular weight:
Structure:

Relevant INDs/NDAs/DMFs: IND 51,188

Drug class: hormone

Indication: hormone replacement therapy

Clinical formulation: patch containing 4.4 mg estradiol and 2.75 mg levonorgestrel

Route of administration: transdermal

Proposed use: HRT

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Safety evaluation:

Safety issues relevant to clinical use: none

Other clinically relevant issues:

Conclusions: No new toxicology was done on estradiol or levonorgestrel and none is needed.

The initial developmental patch used the adhesive matrix — but was changed to — during development to eliminate a potentially toxic compound in —

The developmental patch using — was tested in a variety of in vitro and in vivo tests which included 1) several dermal sensitization studies in guinea pigs 2) several primary irritation studies in rabbits 3) a 7 day cumulative primary skin irritation study in rabbits 4) cytotoxicity test using L-929 mouse fibroblasts. No unusual toxicity, sensitization or irritation was seen in any test.

The adhesive matrix of the to be marketed patch — was evaluated in three studies, a local and systemic tolerance study in rats, a modified maximization test in guinea pigs and a local tolerance test in rabbits.

— is a — consisting of the — acrylate. The toxicology of the — is well documented in the literature and no new toxicology studies are needed.

No local or systemic intolerance of the placebo patch containing — was seen in rats following topical application for 4 wks.

The sensitization potential of the patch was determined following topical application to guinea pigs in a nodified maximization test. No contact sensitization was observed following application of either E2/LNG TDS or placebo patch. Punctiform and striate reddenings in the patch areas, seen at 26 hrs after challenge patch removal, were not present 50 hrs after removal and were attributed to mechanical manipulation during application of the patches.

The local tolerance of the patch contain — was determined following a single 4 hr application to intact skin of male and female rabbits. One hr after patch removal, no clear signs of local intolerance were observed. There were no changes in body weights.

The sponsor states that the final formulation of — did not induce gene mutations in bacteria in the absence or presence of extrinsic metabolic activation at concentrations up to those at which ppt occurred. However, those data were not submitted to the NDA.

— is the — in the final formulation adhesive, — The acute dermal toxicity of — was evaluated in male and female rats. Following topical application of a single dose of 2000 mg/kg (occluded for 6 hrs), there were multifocal and dry scabs in one male on days 8 to 11. When applied to male and female rats at topical doses of 200, 400 or 600 mg/kg (occluded for 6 hrs/dose) once daily for 10 or 11 consecutive days, no target organs of toxicity were identified. Mild dermal changes were observed at all dose levels. Epidermal hyperplasia (one male) and hyperkeratosis (two males and two females) were seen at the high dose. No other treatment related effects were seen.

— studies were conducted to assess the biocompatibility of the polyester — liner and the polyethylene backing film. The materials passed all biocompatibility tests. No evidence of systemically toxic or locally irritating — was observed when — lining and backing materials used in the TDS were administered IV, IP or SC to male mice and female rabbits.

Communication review:

Labeling review: Label should conform to other estrogen/progestogen labels.

RECOMMENDATIONS: ClimaraPro is approvable from standpoint of Pharmacology.

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

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/s/

Alexander W. Jordan
6/14/01 01:12:22 PM
PHARMACOLOGIST