CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-038s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-038**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**May 4, 2006**
PRODUCT:	**Divigel (estradiol 0.1% gel)**
INTENDED CLINICAL POPULATION:	**For treatment of vasomotor symptoms** (b) (4) **associated with menopause**
SPONSOR:	**Upsher-Smith Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Vol. 2, 3, 4, 9, and 10 of 130**
REVIEW DIVISION:	**Division of Urologic and Reproductive Products (HFD-580)**
PHARM/TOX REVIEWER:	**Leslie McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**George Lyght, R. Ph.**

Date of review submission to Division File System (DFS): September 30, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approval

NDA 22-038 (Divigel®, Estradiol Gel 0.1%) has been submitted by Upsher-Smith Laboratories, Inc. for the treatment of vasomotor symptoms (b) (4) associated with menopause. It is administered as a transdermal gel and is packaged into 0.25 g, 0.5, or 1.0 g single-dose sachets containing 0.25 mg, 0.5 mg or 1.0 mg estradiol, respectively. Estradiol Gel, 0.1%, was first approved in Finland (Orion Pharma) in 1994 and has been marketed under various trade names (Divigel®, Sandrena®, Ercostrol®) in over 30 countries.

B. Recommendation for nonclinical studies: none

Characterization of the nonclinical pharmacology and toxicology of Divigel®, Estradiol Gel 0.1% is adequate.

C. Recommendations on labeling: none

There are no pharm/tox recommendations for changes in the current labeling.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The nonclinical toxicology of estradiol is well understood. The sponsor submitted 5 single-dose oral toxicity studies, conducted in mice between 1981 and 1996 as historical documentation of nonclinical testing. Because estradiol has been well studied in animals and humans, and its effects are considered general knowledge, no new repeat-dose toxicity, genotoxicity, carcinogenicity, or reproductive and developmental nonclinical toxicity studies were submitted.

Because Divigel® is a topical product, nonclinical testing of Divigel® focused on determining whether there was any toxicity by that route of administration. The sponsor submitted 9 local tolerance studies covering dermal irritation, dermal sensitization, ocular irritation, phototoxicity, and photosensitization, and 3 studies examining toxicity of leachable compounds from the gel packet. Divigel® was found to have minimal or no significant toxicity in any of these studies.

B. Pharmacologic activity

The pharmacological properties of Estradiol Gel, 0.1% are same as oral estrogens. The main difference between transdermally applied and oral estrogens is the pharmacokinetic profile. Dermally absorbed estradiol avoids first-pass metabolism in the gut wall and the liver.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

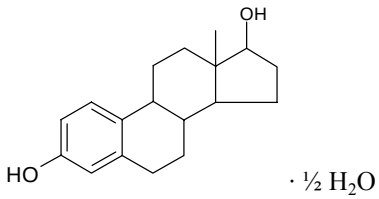
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-038
Review number: 1
Sequence number/date/type of submission: 000 / May 4, 2006 / original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Upsher-Smith Laboratories, Inc., Maple Grove, MN
Manufacturer for drug substance: estradiol is purchased from either of two suppliers: [redacted] (b) (4)

Reviewer name: Leslie McKinney, PhD
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: Sept. 15, 2006

Drug:

Trade name: Divigel
Generic name: estradiol (USP) or estradiol hemihydrate
Code name: USL-221, PFJ-17
Chemical name: estra-1,3,5(10)-triene-3,17β-diol
CAS registry number: not stated
Molecular formula/molecular weight: $C_{18}H_{24}O_2 \cdot ½\ H_2O$ / 281.4
Structure:



$\cdot ½\ H_2O$

Relevant INDs/NDAs/DMFs: IND for this product: 51,246
(reviewed by Lynnda Reid, Ph.D.)
NDAs for related products: NDA 21-166 Estrogel (0.06% estradiol topical gel)
NDA 21-371 Estrasorb (0.25% topical emulsion)
DMFs: DMF [redacted] (b) (4)
DMF [redacted] (b) (4)

Drug class: estrogen

Intended clinical population: For treatment of vasomotor symptoms [redacted] (b) (4) associated with menopause.

Clinical formulation: (sponsor's table, Module 2 vol 1 p 29)

Ingredient	Complies with USOP/NF specifications	Function	Formulation USL-221/ EF108 0.1% gel (mg/g)	Amount per 0.25 g dose (mg)	Amount per 0.5 g dose (mg)	Amount per 1.0 g dose (mg)
Estradiol	Estradiol, USP	Active ingredient	1.0*	0.25	0.5	1.0
Carbomer (b) (4)						
Triethanolamine						
Propylene glycol						
Ethanol (b) (4)						
Purified water						
			Nominal fill	0.25 g	0.5 g	1.0 g

*****Quantity adjusted according to assay and water content

The current formulation, USL-221/EF108, differs from the original (used commercially outside the US from 1994 until 2002/2003) by the type of Carbomer and the type of (b) (4) used. Carbopol (b) (4) triethanolamine is now used (b) (4). The sponsor's table of the development formulations used in clinical and non-clinical studies is included in the Appendix. All excipients are used in FDA-approved products.

Drug substance impurities listed in the DMF: (b) (4)

Route of administration: Transdermal gel; estradiol gel is packaged into 0.25 g, 0.5 , or 1.0 g single-dose sachets containing 0.25 mg, 0.5 mg or 1.0 mg esteradiol, respectively.

Background:

Estradiol Gel, 0.1%, was first approved in Finland (Orion Pharma) in 1994 and has been marketed under various trade names (Divigel®, Sandrena®, Ercostrol®) in over 30 countries. The primary approved indication is for hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women, but in some countries, an additional indication for prevention of postmenopausal osteoporosis has also been granted.

The recommended daily dose varies between 0.5 and 1 g/day, which corresponds to 0.5 and 1 mg estradiol. If combined with progestin for the last 10-14 days of the cycle, withdrawal bleeding will occur in women who have not undergone a hysterectomy.

The pharmacological properties of Estradiol Gel, 0.1% are same as oral estrogens. The main difference between transdermally applied and oral estrogens is the pharmacokinetic profile. Dermally absorbed estradiol avoids first-pass metabolism in the gut wall and the liver.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

All studies are located in Module 4, Nonclinical study reports, vol 1, (submission volume 1.9)

Study Title	Study # Page #	Conducting laboratory, location, and date	GLP + QA
Single dose-toxicity			
Acute oral LD50 of estradiol-17-valerate in the NMRI mice	47312 p. 10 (summary)	(b) (4)	not given
Acute oral LD50 of medroxyprogesterone -17-acetate in NMRI mice	47313 p. 16 (summary)		not given
Acute oral LD50 of Divina (estradiol-17-valerate and medroxyprogestone-17-acetate 1:5) in the NMRI mice	47311 p. 22 (summary)		not given
Acute oral toxicity of combination of estradiol valerate and medroxyprogestone acetate in the mouse	F91062700258 p. 29		QA
Acute oral toxicity of estradiol valerate and/or medroxyprogestone acetate in male and female NMRI mice	PT96116070006 p. 50		GLP + QA
Local tolerance			
Irritant effects on rabbit skin following repeated application (original formulation)	920886D (b) (4) 48/SE p. 76		GLP + QA
Skin sensitization in the guinea pig (original formulation)	920763D (b) (4) 47/SS p. 110		GLP + QA
Estradiol 0.1% gel EF108, skin sensitization to the guinea pig (Buehler method – 9 inductions)(EF108)	ORP 0650/013440/SS p. 132		GLP + QA
Ocular irritation test of PFJ-17 in rabbits (EF108)	P020493 p. 161		Reliability assurance form
Primary skin irritation test on normal and abraded skin in rabbits (EF108) (Summary paragraph only)	P020492 p. 215		not given
Cumulative skin irritation test on normal and abraded skin in rabbits (EF108) (Summary paragraph only)	P020494 p. 222		not given
Skin sensitization (adjuvant and patch) in guinea pigs (EF108) (Summary paragraph)	P020495 p. 227		not given
Skin phototoxicity test in guinea pigs (EF108) (Summary paragraph only)	P020496 p. 232		not given
Skin photosensitization test in guinea pigs (EF108) (Summary paragraph only)	P020497 p. 237		not given
Biological reactivity studies			
Divigel 0.1% gel 0.25g with impurities and Divigel 0.1% gel 0.5 g without impurities cytotoxicity test-elution method (b) (4))	ORP 0116/053228 p. 243		GLP + QA
(b) (4)	(b) (4)		GLP + QA
			GLP + QA

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Estradiol is the major naturally occurring estrogenic hormone secreted by the human ovary. Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They have direct pharmacologic action through estrogen specific receptors on the uterus, Fallopian tubes and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development and the accretion of fat. They also contribute to the shaping of skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones and pigmentation of the nipples and genitals.

2.6.2.2 Primary pharmacodynamics: Loss of ovarian estradiol secretion after menopause can result in instability of thermoregulation and urogenital atrophy.

2.6.2.3 Secondary pharmacodynamics: Circulating estrogens modulate the pituitary secretion of gonadotrophins LH and FSH through a negative feedback mechanism. Estrogen therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

2.6.2.4 Safety pharmacology: Safety pharmacology studies have not been performed with Divigel. However, the pharmacodynamic characteristics of estradiol administered via the transdermal route is similar to oral estrogens.

2.6.2.5 Pharmacodynamic drug interactions: Drug-drug interaction studies have not been performed with Divigel. See clinical data for oral estrogens.

2.6.3 PHARMACOLOGY TABULATED SUMMARY N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Because the pharmacokinetics of estrogens are well-understood, no additional non-clinical studies were conducted to determine absorption, distribution, metabolism, and excretion in animals, with the exception of one absorption assay that was carried out as part of a local tolerance study (see 2.6.6.7, study #920886D/(b) (4)48/SE)).

2.6.4.2 Methods of Analysis: N/A

2.6.4.3 Absorption: N/A

2.6.4.4 Distribution: N/A

2.6.4.5 Metabolism: N/A

2.6.4.6 Excretion: N/A

2.6.4.7 Pharmacokinetic drug interactions: N/A

2.6.4.8 Other Pharmacokinetic Studies: N/A

2.6.4.9 Discussion and Conclusions: N/A

2.6.4.10 Tables and figures to include comparative TK summary: N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Estradiol is generally considered to be relatively safe for prolonged periods of use even at very high doses. For this NDA, acute oral toxicity of estradiol valerate was evaluated in 5 single-dose toxicity studies in mice, and was found to be very low.

Genetic toxicology: Estradiol has not been found to be genotoxic.

Carcinogenicity: Estrogens have been found to increase the risk of endometrial cancer in women. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the incidences of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

Reproductive toxicology: Estradiol administration is contraindicated during pregnancy or during the immediate postpartum period.

Special toxicology:

- Skin irritation: minimal in rabbit
- Skin sensitization: none in guinea pigs by the Buehler method; present when tested with adjuvant
- Ocular irritation: slight in rabbits
- Photosensitivity and phototoxicity: none in guinea pigs
- Biological reactivity to leachables: minimal acute toxicity after ip administration in mice; no intracutaneous reactivity in rabbit; slight dermal irritation in rabbit at the injection site; high multiples of exposure; probably no safety hazards for humans

2.6.6.2 Single-dose toxicity (reviewed for the original IND by Lynnda Reid, Ph.D.)

Acute Oral LD50 of Estradiol-17-Valerate in NMRI Mice
Module 4, volume 1 p. 10, Study no. 47312 completed in 1981

This study was conducted by Orion Corporation in young NMRI mice of both sexes (17-22g), using the method of Pharmacopoeia Nordica (Vol IV). Estradiol-17-valerate was suspended in 0.5% methylcellulose and administered to 10 mice/sex in a single gavage dose of 3000 mg/kg (60 mg/ml, 50 ml/kg). Immediately after dosing the animals were observed for any signs of toxicity, and remained under daily observations for 14 days. At the end of this period all animals were killed and subjected to necropsy. There were no deaths or signs of clinical toxicity. The lethal dose for estradiol-17-valerate in mice was determined to be greater than 3 g/kg.

Acute Oral LD50 of Medroxyprogesterone-17-Acetate in NMRI Mice
Module 4, volume 1 p. 16, Study no. 47313 completed in 1981

This study was conducted by Orion Corporation in young NMRI mice of both sexes (17-22g), using the method of Pharmacopoeia Nordica (Vol IV). Medroxyprogesterone-17-acetate was

suspended in 0.5% methylcellulose and administered to 10 mice/sex in a single gavage dose of 3000 mg/kg (60 mg/ml, 50 ml/kg). Immediately after dosing the animals were observed for any signs of toxicity, and remained under daily observations for 14 days. At the end of this period all animals were killed and subjected to necropsy. There were no deaths or signs of clinical toxicity. The lethal dose for medroxyprogesterone-17-acetate in mice was determined to be greater than 3 g/kg.

Acute Oral LD50 of Divina (estradiol-17-valerate + medroxyprogesterone-17-acetate, 1:5) in NMRI Mice Module 4, volume 1 p. 16, Study no. 47311 completed in 1981.

This study was conducted by Orion Corporation in young NMRI mice of both sexes (17-22g), using the method of Pharmacopoeia Nordica (Vol. IV). Estradiol-17-valerate (2 mg) and medroxyprogesterone-17-acetate (10 mg) were suspended in 0.5% methylcellulose and administered to 10 mice/sex in a single gavage dose of 6000 mg/kg (300 mg/ml, 20 ml/kg). Immediately after dosing the animals were observed for any signs of toxicity, and remained under daily observations for 14 days. At the end of this period all animals were killed and subjected to necropsy. There were no deaths or signs of clinical toxicity. The lethal dose for estradiol-17-valerate/medroxyprogesterone-17-acetate (1:5) in mice was determined to be greater than 6 g/kg.

Acute Oral Toxicity of Combination of Estradiol Valerate and Medroxyprogesterone in the Mouse Module 4, volume 1 p. 30, Study no. F91062700258, completed 1991

This study was conducted by Orion Corporation in 7-8 week old NMRI mice of both sexes. Estradiol-17-valerate and medroxyprogesterone-17-acetate were suspended 1:10 in 1.2% methylcellulose and administered to 5 mice/sex in a single gavage dose of 200/2000 mg/kg, respectively. Immediately after dosing the animals were observed for any signs of toxicity, and remained under daily observations for 14 days. At the end of this period all animals were killed and subjected to necropsy. The only observable effect was a marginal effect on body weight gain: treated mice gained 13% less weight than control mice during the 14-day observation period. There were no other macroscopic signs of clinical toxicity.

Acute Oral Toxicity of Combination of Estradiol Valerate and/or Medroxyprogesterone Acetate in Male and Female NMRI Mice Module 4, volume 1 p. 50, Study no. PT96116070006, completed in 1996

This study was conducted by Orion Corporation in young NMRI mice (males: 25-35g; females: 19-27g). Estradiol-17-valerate and medroxyprogesterone-17-acetate alone at 5 g/kg each or together at a 1:10 ratio (0.45 and 4.55 g/kg, respectively) in 1.2% methylcellulose were administered to 5 mice/sex/group. Immediately after dosing the animals were observed for any signs of toxicity, and remained under daily observations for 14 days. At the end of this period all animals were killed and subjected to necropsy. There were no deaths or signs of clinical toxicity. Histologic examinations were not performed.

2.6.6.3 Repeat-dose toxicity : no new studies submitted

2.6.6.4 Genetic toxicology : no new studies submitted

2.6.6.5 Carcinogenicity : no new studies submitted

2.6.6.6 Reproductive and developmental toxicology : no new studies submitted

2.6.6.7 Local tolerance

Study Title: Irritant Effects on Rabbit Skin Following Repeated Application

Key study findings: minimally irritating

Study no.: 920886D/ (b) (4) 48/SE
Volume #, and page #: Module 4 Vol 1 p 76
Conducting laboratory and location: (b) (4)
Date of study initiation: July 23, 1992
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Divigel 0.1% - SD001 1.04 mg/g; Placebo gel - MVS02-S01,
Formulation/vehicle: clinical formulation

Methods
Doses: 0.25 ml Divigel 0.1% or placebo gel

Study design: New Zealand White rabbits (5/sex/group) weighing 2.5 to 2.8 kg and approximately 11 to 12 weeks of age were treated topically for 28 consecutive days. Approximately 24 hours prior to the first application, hair was removed from the dorsolumbar region exposing an area of skin approximately 15 cm x 10 cm. Clipping was repeated as required during the course of the study. Each test substance was applied and rubbed into one area of skin approximately 4 cm x 4 cm, one on the left flank and the other on the right flank. The animals were not restrained but were fitted with collars for ~6 hours after treatment each day to prevent ingestion of the test substance.

Animals were observed immediately prior to each application and 24 hours after the final application. Erythema and eschar, and edema were scored on a scale of 0 to 4. Blood samples were taken from all animals 3 hours after treatment on day 28 and analyzed for estradiol (pg/ml) using (b) (4) test kit. As control animals were not present in the study and none of a similar age/weight from the same supplier were available in stock, blood samples from untreated (3/sex) were obtained and assayed 5 days after the test animals.

On day 29, the animals were killed by an intravenous overdose of sodium pentobarbitone and samples of treated and untreated skin were prepared for histological examination.

Results: Divigel 0.1% and the placebo gel both produced signs of dermal irritation during the course of the study, however there was evidence that the animals were becoming tolerant and the overall response was reduced at the end of the study. Evidence of a slight dermal response was observed in three animals treated with the placebo gel following 3 applications. By Day 7 nine animals were reacting and by Day 9 all 10 animals showed a slight to well-defined response. A similar level of reaction persisted for the remainder of the study, although over the last few days there was an overall slight reduction in response.

Divigel 0.1% elicited a slight to well-defined reaction in seven animals following 3 applications and in all ten animals by Day 7. As with the placebo, this level of reaction was maintained over the remainder of the study with a similar slight reduction in the overall level of response during the last few days of the study.

In general, histopathological examination of skin samples at the end of the study revealed no significant difference between untreated and treated skin or between drug and placebo treated skin. In two rabbits (one male and one female) treated with Divigel 0.1%, a later stage in the hair cycle was noted compared to sites receiving the placebo gel. The significance of this finding is unclear.

Estradiol levels in untreated animals were ≤5 pg/ml. In animals treated with Divigel 0.1%, estradiol levels ranged from 72 to 309 pg/ml (mean = 210) in males, and 100 to 957 (mean = 330) in females.

Additional local tolerance tests:

Two additional local tolerance tests were submitted in summary form only. They were sponsored by (b) (4) and carried out at (b) (4) in 2003. Because no original data were submitted, the reviewer cannot vouch for the adequacy of the tests.

Primary skin irritation test on normal and abraded skin in rabbits (EF108) Study # P020492	PFJ-17 (1.0 g) and PFJ-17B (1.0 g) administered to New Zealand white rabbits (N=6F/gp). No skin reactions were observed in either healthy or abraded skin. Primary irritant index (PII) was 0 in all cases and severity of skin irritation was evaluated as 'slight'. Sponsor concludes no primary skin irritancy on rabbit skin.
Cumulative skin irritation test on normal and abraded skin in rabbits (EF108) Study # P020494	PFJ-17 (1.0 g) and PFJ-17B (1.0 g) administered to New Zealand white rabbits (N=6F/gp) for 28-days. Very slight erythema (score 1) was observed in healthy and abraded skin in 2 subjects between day 3 and 9. Mean value throughout was 0.06 for PFJ-17 and 0.04 for PFJ-17B. Degree of irritancy was evaluated as 'slight' and transient.

2.6.6.8 Special toxicology studies

Study Titles: Skin Sensitization in the Guinea-Pig and Estradiol 0.1% Gel EF108, Skin Sensitization to the Guinea Pig (Buehler Method - 9 Inductions)

Key study findings: This review covers two identical, independent sensitization tests conducted 9 years apart that compare the original and the current, to-be-marketed formulation. Both tests were negative. Estradiol 0.1% gel was considered not to be a contact sensitizer based on this assay.

Study no.: 920763D/(b) (4) 47/SS and ORP 065/013440/SS
Volume #, and page #: Module 1 vol 1 p 110 and p. 132
Conducting laboratory and location: (b) (4)
Date of study initiation: July 8, 1992 and May 31, 2001
GLP compliance: yes
QA reports: yes (x) no ( )

Drug, lot #, and % purity: SD 001, 0.1%
Formulation/vehicle: clinical formulation

Methods
Doses: Divigel 0.1%, as supplied for both induction and challenge

Study design: The study was performed in accordance with the OECD Guideline for Testing of Chemicals No. 406 "Skin Sensitization" (adopted 5/12/1981), and according to the delayed Guinea-pig contact hypersensitivity assay in described by Buehler (Arch. Dermatol., 1965, 91:171). Tests were performed in female albino Dunkin/Hartley guinea pigs (10/group; more recent test used 20 in the test group, 10 control).

Induction: Prior to each induction application, the skin on the left shoulder region was clipped free of hair. A 20 x 20 mm patch of surgical gauze (3 layers thick) was saturated with approximately 0.5 ml of Divigel 0.1% or placebo gel and placed on the skin. Sites were covered by a length of impermeable plastic adhesive tape and secured by elastic adhesive bandages wound round the torso and fixed with plastic adhesive tape. Contact with the skin was maintained for ~6 hours/exposure. Dressing were then removed and the resulting dermal reactions assessed ~24 hours later. A total of 9 induction applications were made, 3/week for 3 weeks on alternating days of the week.

Challenge: The control and test animals were challenged topically 2 weeks after the final induction application using Divigel 0.1%. Hair was removed from a 50 x 50 mm area on the right flank of each animal. A 20 x 20 mm gauze patch was saturated with approximately 0.5 ml of the test substance and applied in the manner used for the induction applications. Patches were removed after 6 hours and dermal responses were assessed at 24, 48 and 72 hours for erythema and eschar formation, and edema.

A test animal was considered to show positive evidence of delayed contact hypersensitivity if the observed dermal reaction at challenge was definitely more marked and/or persistent than the maximum reaction seen in controls.

Results: Divigel 0.1% did not produce evidence of skin sensitization in any of the test animals.

Additional skin sensitization study using adjuvant:

An additional skin sensitization test was submitted in summary form only. It was sponsored by (b) (4). and carried out at (b) (4) in 2003. Because no original data were submitted, the reviewer cannot vouch for the adequacy of the test.

Skin sensitization (adjuvant and patch) in guinea pigs (EF108) Study #P020495	Skin sensitization of PFJ-17 (1.0 g) and PFJ-17B (1.0 g) was studied using the adjuvant and patch test method on female guinea pigs. The positive reference for 2,4-dinitrochlorobenzene (DNCB; 0.5% w/v). PFJ-17 was found to have skin sensitization under experimental conditions using an adjuvant.

Study title: Ocular irritation test of PFJ-17 in rabbits (EF108).

Key study findings: Estradiol was found to have a slight degree of ocular irritancy in the rabbit.

Study no.: P020493
Volume # and page #: Module 4 Vol 1 p 161
Conducting laboratory and location: (b) (4)

Date of study initiation: Sept. 25, 2002
GLP compliance: Statement of compliance with Ordinance 21 of the Ministry of Health, Welfare and Labor, which sets performance standards for non-clinical studies.
QA reports: yes (X) no ( ) A reliability assurance form was submitted
Drug, lot #, and % purity: PFJ-17 (active), lot # CFC21B and PFJ-17B (placebo), lot # CH010L2B provided by (b) (4).
Formulation/vehicle: A full analysis of the composition of PFJ-17 and 17B were provided but the clinical formulation number is not given in any of the study reports conducted by (b) (4). The sponsor identifies the formulation as EF108, which is the current formulation, in the study titles listed in the Table of Contents for Nonclinical Study Reports.

Methods

Doses: Test article or placebo were administered at 0.1 mL/site. Among 9 animals, 6 animals were not treated by washing, and 3 animals received washing of eyes with 20 mL of purified water for ~30 sec after 30 sec of eye drop treatment. The left eye served as the control.

Study design: Tests were conducted on New Zealand white rabbits (F), 3 months old, weighing 2.63-3.03 kg, N=9/gp (6 with washed eyes, and 3 with non-washed eyes). Changes in cornea, iris, and conjunctivae were observed at 1, 24, 48, 72, and 96 hrs post-treatment, and reactions scored using the Draize assessment criteria. Corneal damage was also assessed using a slit lamp.

Results: Erythema and edema of the conjunctiva were observed 1 hr following administration, but began to lessen after 24 h, and resolved at 72 h. Corneal stains were observed at 24 h and resolved by 96 h. No changes in the iris were observed. Mean total irritation scores were maximal at 1 hr and resolved by 72 h for both test article and placebo. Out of a possible score of 110, estradiol gel vs placebo was scored 9.0:8.0 for animals not receiving eye wash and 6.7:6.0 for animals receiving eyewash. Based on these results, estradiol gel was graded as having a mild degree of ocular irritancy.

Additional special toxicology studies: phototoxicity and photosensitization
Phototoxicity and photosensitization tests were submitted in summary form only. They were sponsored by (b) (4) and carried out a (b) (4) in 2003. Because no original data were submitted, the reviewer cannot vouch for the adequacy of the tests.

Skin phototoxicity test in guinea pigs (EF108) Study # P020496	Skin phototoxicity of PFJ-17 (active, 1.0 g) and PFJ-17B (placebo, 1.0 g) were studied using female Hartley guinea pigs. The positive reference was 8-methoxypsoralen (8-MOP) in a medium of acetone. No skin reactions were observed throughout the observation periods following irradiation with UV light. Phototoxicity was judged negative. Response to the positive control was appropriate and animals were judged reactive.
Skin photo-sensitization test in guinea pigs (EF108). Study # P020497.	Skin photosensitization of PFJ-17 (active, 1.0 g) and PFJ-17B (placebo, 1.0 g) was studied using the Horio method on female Hartley guinea pigs. The positive reference was 3,3',4'5-tetrachlorosalicylanilide (TCSA) in a medium of ethanol. No skin reactions were observed for either test article or placebo for photosensitized groups. Photosensitization was judged negative. Response to the positive control was appropriate and animals were judged reactive.

Additional special toxicology studies:

(b) (4)

[redacted]

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2.6.6.9 Discussion and Conclusions

No significant safety concerns were revealed in the toxicology studies submitted by the sponsor in support of this NDA. Toxicology testing is deemed sufficient and no additional testing is required.

2.6.6.10 Tables and Figures N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

From a Pharm/Tox perspective, there are no new safety concerns for approval of Divigel®, Estradiol Gel 0.1%. Contraindications for and complications following use of Divigel® are consistent with those for estrogens as a class and are detailed in the labeling.

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/s/

Leslie McKinney
9/20/2006 11:39:51 AM
PHARMACOLOGIST

Lynnda Reid
9/21/2006 11:42:16 AM
PHARMACOLOGIST