CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-633

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:	**21-633**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**October 14, 2003**
PRODUCT:	**Femtrace™ (estradiol acetate tablets)**
INTENDED CLINICAL POPULATION:	**postmenopausal women**
SPONSOR:	**Galen Ltd., Rockaway, NJ**
DOCUMENTS REVIEWED:	**Vols. 8, 9 and 10**
REVIEW DIVISION:	**Division of Reproductive and Urologic Drug Products (HFD-580)**
PHARM/TOX REVIEWER:	**Lynnda Reid, Ph.D., Supervisory Pharmacologist/Toxicologist**
DIVISION DIRECTOR:	**Daniel Shames, M.D.**
PROJECT MANAGER:	**Jennifer Mercier**

Date of review submission to Division File System (DFS): June 28, 2004

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: From a Pharmacology/Toxicology perspective, we recommend approval of this NDA based on the established safety of estradiol at equivalent or higher doses.

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling: Labeling should be consistent to other drugs containing estrogen/estradiol derivatives.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Estradiol-3-acetate is quickly hydrolyzed *in situ* to estradiol with no significant systemic exposure to estradiol-3-acetate. The safety of estradiol-3-acetate is therefore based on studies performed with estradiol. Adverse effects are similar across species (i.e., rodents, dogs and monkeys) and are generally associated with its pharmacologic activity, e.g., effects on sexual and reproductive organs (primary and secondary) including blockage of spermatogenesis in males, endometrial and uterine hyperplasia and mammary hypertrophy in females; and increased pituitary and adrenal gland weight. Hepatomegaly with cholestasis, and hematological effects including anemia, thrombocytopenia and agranulocytosis (particularly in dogs) have also been seen at high doses.

Estradiol is considered non-genotoxic and estradiol-3-acetate was negative in the Ames Assay. There is an increased risk of cancer in humans and animals associated with administered of estrogens. In rodents, the most frequently observed tumors are pituitary and mammary and, less frequently, endometrial carcinomas and ovarian tumors. Hepatic adenomas have also been observed.

In all species, estrogens have a potent abortive effect. In females, estrogens accelerate the migration of the egg and reduce the number of implantations in females. Estrogens also reduce the survival rates of newborns. In prenatal and prepubertal animals, permanent sterility may be induced.

B. Pharmacologic activity: Exogenous estrogens act to reduce the elevated levels of gonadotropins, LH and FSH seen in postmenopausal women.

C. Nonclinical safety issues relevant to clinical use: Use of estradiol has been well characterized in both pre- and postmenopausal women.

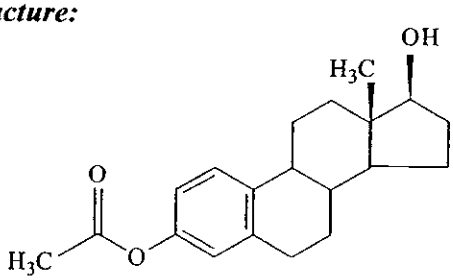
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

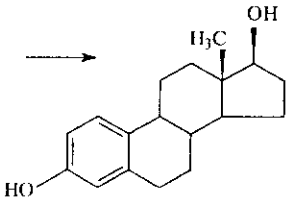
NDA number: 21-633
Review number: 1
Sequence number/date/type of submission: N000 dated October 14, 2003
Information to sponsor: Yes ( ) No (x)
Sponsor: Galen Limited
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866
(973) 442-3229
Manufacturer for drug substance: [ ]

Reviewer name: Lynnda Reid, Ph.D., Supervisory Pharmacologist
Division name: Division of Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: June 28, 2004

Drug: Estradiol Acetate Tablets
Trade name: estradiol acetate; estradiol-3-acetate
Code name: EA, E_3A, and WC2047
Chemical name: 17ß-Estradiol-3-acetate; Estra-1,3,5(10)-triene-3,17ß-diol-3-acetate; and 3-Acetoxy-1,3,5(10)-3stratriene-17ß-ol
CAS registry number: ?
Molecular formula: $C_{20}H_{26}O_3$
Molecular weight: 314.41
Structure:



Estradiol 3 Acetate



Estradiol

Relevant INDs/NDAs/DMFs:

- IND 58,488 and NDA 21-367: Extended release vaginal ring delivery of estradiol acetate at rates nominally equivalent to 0.05 and 0.10 mg estradiol per day.

Drug class: estrogen

Intended clinical population: postmenopausal women with moderate to severe vasomotor symptoms and/or vulvar and vaginal atrophy

Clinical formulation: Estradiol acetate tablets contain E_3A in three strengths: 0.45 mg, 0.9 mg and 1.8 mg per tablet.

Tablet Formulations	Tablets (w/w)		
Estradiol acetate	**0.45 mg**	**0.9 mg**	**1.8 mg**
Iron Oxide Color, NF (Yellow)			
Povidone, USP			
Lactose Monohydrate,			
Microcrystalline Cellulose, NF			
Croscarmellose sodium, NF			
Silicon Dioxide, NF			
Magnesium Stearate, NF			
Acetic Acid, USP			
	*	*	*
Purified Water, USP	*	*	*
TOTAL	90.0 mg	90 mg	90 mg

Drug Product Impurities	% per Tablet		
	0.45 mg	**0.9 mg**	**1.8 mg**
[			
			]
TOTAL	[		]

Route of administration: Oral

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-633 are owned by Galen Ltd. or are data for which Galen Ltd. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-633 that Galen Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Galen Ltd. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-633.

Studies reviewed within this submission:

1) Determination of the Rate of Conversion of Estradiol-3-Acetate to Estradiol *In Vitro* in Human Serum and Human Whole blood using [ ]

2) Reverse Mutation in four Histidine-Requiring Strains of *Salmonella typhimurium* and Two Tryptophan-Requiring Strains of *Escherichia coli*

Studies not reviewed within this submission: Based on the rapid rate of hydrolysis of E_3A to estradiol, Galen plans to rely on nonclinical literature references and clinical data to document the pharmacology and safety of estradiol. Referenced toxicology studies for estradiol include the following: acute and repeat dose toxicity studies in rat and dog; carcinogenicity evaluations in mice, rats, hamsters, and guinea pigs; results from a p53 ± knock-out gene study in mice; and results from a battery of genetic toxicity assays defining the mutagenic potential of estradiol.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Estrogens are largely responsible for the changes which take place in females at puberty and for the maintenance of the menstrual cycle and secondary sexual characteristics. Estrogens exert their effects via specific receptors situated mainly within the nucleus. Estrogen receptors are found primarily in the female genitourinary tract, breast, pituitary, hypothalamus, bone, and liver as well as other tissues. Estradiol is the principal intracellular human estrogen and a substantially more potent receptor agonist than its metabolites, estrone and estriol.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) through negative feedback inhibition.

Drug activity related to proposed indication: Estrogens act to reduce the elevated levels of gonadotropins, LH and FSH seen in postmenopausal women.

2.6.2.3 Secondary pharmacodynamics

Estrogens also play an important role in various metabolic processes, including the modulation of bone resorption and in blood clotting.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Estradiol acetate is considered a prodrug of estradiol. The following studies were performed to verify the rapid hydrolyzes of estradiol-3-acetate to estradiol:

Study No. 1450/011 (RR 06801.2): Determination of the Rate of Conversion of Estradiol-3-Acetate to Estradiol In Vitro in Human Serum and Human Whole Blood using [redacted]

Study No. RR 060703.0: Characterization of Serum Estradiol Acetate Concentration in Serum Samples from Study PR 09601, A Food-Effect Study of 1.8 mg Estradiol Acetate Tablets in Healthy Postmenopausal Women.

The mean K_1 value was 1.48 min^{-1} and the corresponding harmonic mean half-life value was 28 seconds (0.47 minutes). These results indicate that the concentration of estradiol acetate was negligible within 2 minutes (4 half-lives) following absorption. Following oral administration of 1.8 mg estradiol acetate to postmenopausal women, estradiol acetate could not be detected in any of the serum samples analyzed. The studies confirmed that hydrolyzed of estradiol acetate to estradiol is very rapid and the absence of any significant systemic exposures to estradiol acetate.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

No studies were submitted with estradiol-3-acetate. The following is a summary of known effects associated with estradiol (E2) administration.

General toxicology: Chronic administration of estradiol has been evaluated in rodents, dogs and monkeys. Adverse effects are generally associated with the pharmacologic activity of E2 and similar across species, and include the following:

- effects on sexual and reproductive organs (primary and secondary) including blockage of spermatogenesis in males, endometrial and uterine hyperplasia and mammary hypertrophy in females
- increased weight of the pituitary and adrenal glands
- hepatomegaly with cholestasis
- hematological effects including anemia, thrombocytopenia and agranulocytosis (particularly in dogs)

Genetic toxicology: E2 does not cause genetic mutations, nor is it a directly clastogenic agent. At high *in vitro* concentrations it has a spindle poison effect resulting in aneuploidy, however, this effect does not appear to be transposable *in vivo*. NTP considers E2 non-mutagenic.

E_3A was not considered a mutagen under conditions tested in the standard Ames Assay.

Carcinogenicity: There is an increased risk of cancer in humans and animals administered exogenous estradiol. In rodents, the most frequently observed tumors are pituitary and mammary and, less frequently, endometrial carcinomas and ovarian tumors. Hepatic adenomas have also been observed.

Reproductive toxicology: Fertility in males is inhibited due to the blockade of spermatogenesis. In females, E2 accelerates the migration of the egg and reduces the number of implantations. In prepubertal animals, permanent sterility may be induced.

In all species, E2 has a potent abortive effect. At doses which do not induce abortion, major abnormalities of the reproductive apparatus of the offspring are observed including sterility, as well as teratogenic effects in other area of the body, e.g., cleft palate. E2 also reduces the survival rates of newborns.

2.6.6.2 Single-dose toxicity

No studies were submitted with estradiol acetate.

2.6.6.3 Repeat-dose toxicity

No studies were submitted with estradiol acetate.

2.6.6.4 Genetic toxicology

Study no.: Reverse Mutation in four Histidine-Requiring Strains of *Salmonella typhimurium* and Two Tryptophan-Requiring Strains of *Escherichia coli*

Key findings: Under the conditions tested, E_3A was not considered to be mutagenic.

Study no.: CR 04703
Volume #, and page #: Vol. 8, page 209
Conducting laboratory and location: [redacted]
Date of study initiation: April 15, 2003
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: 9411306 (M5002)

Methods and Results: See tabulated study report (Sponsor's Tablee 2) on the following page.

Study validity: Positive controls performed as expected.

Study outcome: Negative

2.6.6.5 Carcinogenicity

No studies were submitted with estradiol acetate.

2.6.6.6 Reproductive and developmental toxicology

No studies were submitted with estradiol acetate.

2.6.6.7 Local tolerance

No studies were submitted with estradiol acetate.

2.6.6.8 Special toxicology studies

No studies were submitted with estradiol acetate.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None Submitted

Table 2. Estradiol Acetate Ames Study Tabulated Study Synopsis

Name of Company: Galen Limited Name of Finished Product: Estradiol Acetate Name of Active Substance(s): Estradiol Acetate	TABULAR FORMAT NDA 21-633
Bacterial Reverse Mutation Assay (Report No. CR 04703) Report date: 14 June 03 Study period (years): 15 April – 20 May 03	
Test cells:	*Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) *Escherichia coli* (WP2 uvrA)
Test for induction of:	Bacterial reverse mutation
Metabolizing system:	± Aroclor 1254-induced rat liver post-mitochondrial fraction (S9)
Formulation of test substance and final concentration:	Test article: Solution of estradiol acetate (EA) (batch no. 9411306*) dissolved in dimethylsulfoxide (DMSO), 0.15-5000 µg/plate Reference compound: Solution of estradiol hemihydrate (E) (batch no. 00005013) in DMSO, 0.15-5000 µg/plate
Treatment and recovery time:	Toxicity range-finder experiment: incubation at 37°C in the dark for 3 days. Additional pre-incubation step in mutation experiments: 1 hour at 37°C.
Formulation of positive controls and final concentrations:	2-nitrofluorene (1.0 µg/plate), sodium azide (1.0 µg/plate) 9-aminoacridine (75.0 µg/plate), methyl methanesulfonate (1000 µg/plate and 2.0 µg/plate) and 2-aminoanthracene (1.0 µg/plate + S9, Salmonella strains; 10.0 µg/plate +S9, WP2uvrA)
No. replicate cultures:	3
RESULTS: Cytotoxic Effects: EA background lawn toxicity in the initial toxity-mutation assay began at 500 (-S9) or 5000 µg/plate (+S9) for *Salmonella* and *E. coli*. E did not produce any background lawn toxicity at dosages as high as 5000 µg/plate for *Salmonella* and *E. coli*. Genotoxic Effects: EA did not produce any positive mutagenic responses with any of the tester strains (+S9). Dosages as high as 5000 µg/plate (*Salmonella*, +S9; *E.coli*, -S9), and as high as 1500 µg/plate (TA98, TA100, TA1535 & TA1537, -S9). E did not produce any positive mutagenic responses at dosages as high as 5000 µg/plate with any of the tester strains (±S9).	
CONCLUSIONS: Under the conditions of this study, EA and E were concluded to be negative in the Bacterial Reverse Mutation Assay.	
Study conducted by the applicant: ☐ Yes ☑ No	
If 'no', indicate the name and address of the institute that conducted the study: C] Study in compliance with GLP: ☑ Yes ☐ No ☐ Not required.	

* Referred to in the final study report by its Galen material log number, M5002.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Due to the rapid *in situ* hydrolysis of estradiol acetate to estradiol, estradiol acetate is considered a prodrug for estradiol with a similar pharmacologic and toxicologic profile.

Unresolved toxicology issues (if any): none

Recommendations: NDA approval

Suggested labeling: Labeling should be consistent with current estrogen class labeling.

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/s/

Lynnda Reid
6/28/04 01:17:53 PM
PHARMACOLOGIST

45 Day NDA Meeting Checklist
Pharmacology/Toxicology

NDA Number: 21-633
Drug Name: Femtrace™ (estradiol acetate tablets)
Sponsor: Galen (Chemicals) Limited

Date: November 3, 2003
Reviewer: Lynnda Reid, Ph.D.

Date CDER Received: October 20, 2003
Filing Date: December 19, 2003
User Fee Date: August 20, 2004
Expected Date of Draft Review: May 1, 2004

On initial overview of the Pharm/Tox portion of the NDA application

1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	YES	
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	YES	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?	YES	
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	YES	
5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	YES	
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	YES	

7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	NA	Filed under 505(b)
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	NA	Filed under 505(b)
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	YES YES NA	Standard labeling for estrogen drug products
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	
11)	Reasons for refusal to file:		

Lynnda Reid, Ph.D.
Reviewing Pharm/Tox Reviewer

Suzanne Thornton, Ph.D.
Acting Pharm/Tox Supervisor

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

/s/

Lynnda Reid
12/2/03 11:26:56 AM
PHARMACOLOGIST

Suzanne Thornton
12/2/03 11:29:38 AM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

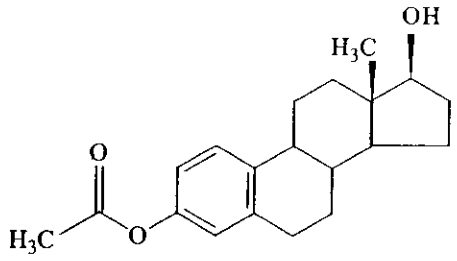
IND No.: 63,188
Review number: Pre-NDA
Sequence number/date/type of submission: N018 (GC) dated January 9, 2003

Reviewer: Lynnda Reid, Ph.D.
Division: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: January 23, 2003

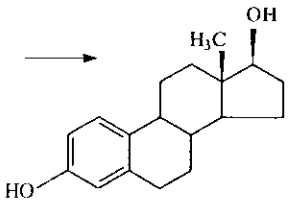
Sponsor: Galen Limited
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866
(973) 442-3229

Manufacturer for drug substance: C]

Drug: Estradiol Acetate Tablets
Trade name: estradiol acetate; estradiol-3-acetate
Code name: EA, E_3A, and WC2047
Chemical name: 17ß-Estradiol-3-acetate; Estra-1,3,5(10)-triene-3,17ß-diol-3-acetate; and 3-Acetoxy-1,3,5(10)-3stratriene-17ß-ol
CAS registry number: ?
Molecular formula: $C_{20}H_{26}O_3$
Molecular weight: 314.41
Structure:



Estradiol $_3$ Acetate



Estradiol

Relevant INDs/NDAs/DMFs:
- IND 58,488 and NDA 21-367: Extended release vaginal ring delivery of estradiol acetate at rates nominally equivalent to 0.05 and 0.10 mg estradiol per day.

Drug class: estrogen

Indication: 1) Treatment of moderate to severe vasomotor symptoms associated with menopause
2) Treatment of vulvar and vaginal atrophy

Clinical formulation: Estradiol acetate tablets contain E_3A in three strengths: 0.45 mg, 0.9 mg and 1.8 mg per tablet.

Tablet Formulations	Tablets (w/w)		
Estradiol acetate	**0.45 mg**	**0.9 mg**	**1.8 mg**
Iron Oxide Color, NF (Yellow)			
Povidone, USP			
Lactose Monohydrate,			
Microcrystalline Cellulose, NF			
Croscarmellose sodium, NF			
Silicon Dioxide, NF			
Magnesium Stearate, NF			
Acetic Acid, USP			
	*	*	*
Purified Water, USP	*	*	*
TOTAL	90.0 mg	90 mg	90 mg

Drug Product Impurities	% per Tablet		
	0.45 mg	**0.9 mg**	**1.8 mg**
TOTAL			

Route of administration: Oral

Proposed clinical protocol: intended for oral consumption once daily

Introduction and drug history: Estradiol-3-acetate (E_3A) is a prodrug of estradiol. Estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. E_3A is a prodrug which is rapidly hydrolyzed to estradiol and is approximately 1.15 times as bioavailable as oral estradiol.

Date of Pre-NDA Team Meeting: February 10, 2003 (11:00 a.m.)
Date of Pre-NDA Meeting: February 12, 2003 (9:30 a.m.)

Previous clinical experience:

- Under IND 63,188, safety and efficacy have been evaluated in clinical studies with oral estradiol acetate at doses of 0.45, 0.9 and 1.8 mg/day for up to 12 weeks.

- Estradiol acetate has been evaluated in a vaginal ring delivery system (LOTRACE VR, NDA 21-367) with release rates nominally equivalent to 0.05 and 0.10 mg estradiol per day. Therapy is usually initiated with LOTRACE VR 0.05 mg/day, inserted vaginally once every 3 months.

Completed Nonclinical Studies:

1) Determination of the Rate of Conversion of Estradiol-3-Acetate to Estradiol *In Vitro* in Human Serum and Human Whole blood using [redacted]

2) Reverse Mutation in four Histidine-Requiring Strains of *Salmonella typhimurium* and Two Tryptophan-Requiring Strains of *Escherichia coli*

Future Nonclinical Development Plans (Item 5): None. Based on the rapid rate of hydrolysis of E_3A to estradiol, Galen plans to rely on nonclinical literature references and clinical data to document the pharmacology and safety of estradiol. Referenced toxicology studies for estradiol will include the following: acute and repeat dose toxicity studies in rat and dog; carcinogenicity evaluations in mice, rats, hamsters, and guinea pigs; results from a p53 ± knock-out gene study in mice; and results from a battery of genetic toxicity assays defining the mutagenic potential of estradiol.

OVERALL SUMMARY AND EVALUATION:

Safety evaluation: E_3A is quickly hydrolyzed *in situ* to estradiol. Estradiol is the principal intracellular human estrogen and is currently available in numerous approved drug products at concentrations comparable or higher than those anticipated following clinical use of E_3A.

Safety issues relevant to clinical use: none

Future development or issues: none

SPECIFIC QUESTION PERTAINING TO NONCLINICAL STUDIES:

Question 2. Does the Agency concur with the content and outline proposed for Item 5?

Question 3. Does the Agency concur that a literature survey of the pharmacology and toxicology of estradiol fulfills the requirements for Item 5?

Agency Response: Yes, provided the rapid hydrolysis of estradiol acetate to estradiol has been substantiated in pharmacokinetic data collected in clinical studies.

Question 9. Does the Agency concur that only the following two types of components need to be submitted in the NDA in electronic format?

- individual patient data in SAS transport file format for the pivotal clinical studies
- draft labeling in MS WORD 2000 and PDF files

Agency Response: Yes. However, although not required electronic submission of the Pharm/Tox executive summary in either Word or PDF format would be greatly appreciated. Complete, readable hard copies of all referenced literature should be submitted.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

cc: list:
IND 63,188
HFD-580
HFD-580/Pharm/Reid
HFD-580/Pharm/Jordan
HFD-580/CSO/Lyght
HFD-580/MO/Van der Vlugt

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/s/

Lynnda Reid
2/13/03 04:28:40 PM
PHARMACOLOGIST

Alexander W. Jordan
2/20/03 02:22:59 PM
PHARMACOLOGIST