CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021463Orig1s000

PHARMACOLOGY REVIEW(S)

Memo to the file

Date: 12-16-2010

NDA #: 21-463 Resubmission

Date of submission: 6-30-10

Sponsor: Endo Pharmceuticals

Drug Product: Fortesta (testosterone) gel for topical use CIII

Indication: Subject: Final Label document

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

Regulatory action: The final label received 12-15-10 is acceptable from the P/T perspective.

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/s/

LYNNDA L REID
12/16/2010

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:	21-463 Resubmission
Supporting document:	62eCTD
DATE RECEIVED BY CENTER:	6/3/10
PRODUCT:	Fortigel (testosterone) 2% Gel
INTENDED CLINICAL POPULATION:	Testosterone replacement therapy in male hypogonadism
SPONSOR:	ENDO Pharmaceuticals
REVIEW DIVISION:	Division of Reproductive and Urologic Products
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	Jeannie Roule

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Although this NDA was issued a not approvable letter on 7-3-03 and a complete response on 10-16-09, Pharmacology had recommended approval of the NDA based on extensive preclinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel. From the P/T perspective there are no safety concerns and P/T again recommends approval of the resubmitted NDA.

B. Recommendation for nonclinical studies: No new nonclinical studies are required.

C. Recommendations on labeling: Pending.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: The safety of testosterone is well established based on extensive available preclinical published literature.

B. Pharmacologic activity: Testosterone is an endogenous androgenic hormone.

C. Nonclinical safety issues relevant to clinical use: None

Recommendations: Nonclinical data support approval of the resubmitted NDA 21-463.

Suggested labeling: Under review. Labeling will be consistent with class labeling for testosterone products.

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/s/

KRISHAN L RAHEJA
11/19/2010

LYNNDA L REID
11/19/2010
I concur, nonclinical data supports approval of NDA 21-463.

SUPERVISORY MEMO **FOOD AND DRUG ADMINISTRATION**

Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Date:	October 7, 2009
Reviewer:	Lynnda Reid, Ph.D. Supervisory Pharmacologist
NDA #/SS#/date:	21-463 (S000) 5/4/09
Sponsor:	ProStrakan Inc.
Drug Product:	Testosterone 2% Gel (Fortesta)
Indication:	Testosterone Replacement Therapy in Hypogonadal Males

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Conclusions and Recommendations: I concur with the primary pharmacology/toxicology reviewer, Dr. Krishan Raheja, that nonclinical data support approval of 2% testosterone gel to treat hypogonadal males.

Outstanding nonclinical issues: None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%

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/s/

LYNNDA L REID
10/07/2009

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:	21-463 Resubmission
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	5/4/09
PRODUCT:	Fortigel (testosterone) 2% Gel
INTENDED CLINICAL POPULATION:	Testosterone replacement therapy in male hypogonadism
SPONSOR:	ProStrakan Inc.
DOCUMENTS REVIEWED:	Vol. 1 of 1
REVIEW DIVISION:	Division of Reproductive and Urologic Products (HFD-580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	Jeannie Roule

Date of review submission to Division File System (DFS): 7-10-09

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Although this NDA was issued a not approvable letter on 7-3-03, Pharmacology had recommended approval of the NDA based on extensive preclinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel. From the P/T perspective there are no safety concerns and P/T again recommends approval of the resubmitted NDA.

B. Recommendation for nonclinical studies: No new nonclinical studies are required.

C. Recommendations on labeling: As required the Labeling is in accordance with PLR and provided in SPL format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: The safety of testosterone is well established based on extensive available preclinical published literature.

B. Pharmacologic activity: Testosterone is an endogenous androgenic hormone.

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-463
Review number: 1
Sequence number/date/type of submission: 000/4-17-09/Resubmission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: ProStrakan Inc. Bedminster, NJ
Manufacturer for drug substance: (b) (4)

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D
Division name: Reproductive and Urologic Products
HFD #: 580
Review completion date:

Drug:

Trade name: Fortigel
Generic name: Testosterone 2% gel
Code name: CP601B
Chemical name: 1. 17β-hydroxyandrost-4-en-3-one
2. Androst-4-en-3-one, 17-hydroxy-(17β)-
CAS registry number: 58-22-0
Molecular formula/molecular weight: $C_{19}H_{28}O_2$/288.42

Relevant INDs/NDAs/DMFs: IND (b) (4); DMF (b) (4)

Drug class: Steroid (androgen)

Intended clinical population: Replacement therapy in male hypogonadism (replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone i.e., 1) primary hypogonadism and 2) hypogonadotropic or secondary hypogonadism.

Clinical formulation: gel

Route of administration: topical

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

:

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-463 are owned by ProStrakan Inc. or are data for which ProStrakan, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-463 that ProStrakan Inc. 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 ProStrakan Inc. 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 21-463.

Studies reviewed within this submission: On July 2, 2007, John Kim, PM and this reviewer asked ProStrakan Inc. about possible changes made to the drug substance synthesis or supplier or to the drug product manufacturing procedures and formulation. In response the sponsor confirmed in a latter dated 7-5-07 that there have been no changes in the drug substance synthesis, the supplier or in the drug product manufacturing procedures and formulation from the information submitted by Cellegy, the previous sponsor of this drug.

Regarding an enquiry about additional degradation products, ProStrakan stated that they inserted these in the specifications after thorough review of the work performed by Cellegy. ProStrakan stated that after reviewing the chromatograms generated by the previous sponsor, peaks for 5 additional impurities were discovered. These impurities, which form during the long term storage of Fortigel, were present in previous batches of the drug product but were not reported by Cellegy. These degradation products are not present at product release and are degradants that increase gradually over time.

ProStrakan has identified and quantified these degradants. Three of the degradants were identified as (b) (4) One of the remaining 2 degradants was tentatively identified as a (b) (4) and the other one was below the ICH threshold for identification at 24 months. The levels of theses degradants were calculated retrospectively from the original chromatograms obtained during the stability studies. A drug product specification is therefore proposed by the sponsor with limits based on the levels observed after 24 months storage, the proposed shelf life.

Degradant levels in Fortigel 2% Gel following storage for 24 months at 25 C/60% RH are listed in table below:

Impurity	Identity	% w.r.t. testosterone after 24 months storage. Mean	SD
[redacted] (b) (4)			

* levels at 48 months

Based on ICH guideline Q3B (R2) impurities 1, 2 and 4 exceeded the [redacted] (b) (4) threshold and therefore needed qualification.

Sponsor stated that the degradants of Fortigel 2% Gel can be considered to be qualified on the basis of the patient exposure to the product, up to 40 months, during Phase 3 clinical trials.

Sponsor concluded that the quality of the Fortigel drug product is the same as that used in previous clinical trials and therefore, these newly listed degradants have been adequately qualified. Nonclinical concurs with this assessment.

Overall conclusions and recommendations

Conclusions: Based on pharmacology/toxicology information submitted and reviewed under original NDA dated 5-31-02, there are no safety concerns from the P/T perspective.

Unresolved toxicology issues (if any): None

Recommendations: Nonclinical data support approval of the resubmitted NDA 21-463.

Suggested labeling: Suggested labeling is in accordance with PLR and provided in SPL format.

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/s/

Krishan L. Raheja
7/13/2009 11:05:45 AM
PHARMACOLOGIST

Lynnda Reid
7/13/2009 11:07:03 AM
PHARMACOLOGIST

Memo to the file

Date: 8-1-2002

Subject: NDA 21-463 filling meeting on 7-31-2002

NDA 21-463 – Tostrx (testosterone gel 2%) as testosterone replacement therapy in male hypogonadism is filable from the P/T prospective.

Krishan L. Raheja
P/T Reviewer

N21463.filling/8-1-2002

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/s/

Krishan L. Raheja
8/1/02 03:18:36 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-463
Review number: 001
Serial number/date/type of submission: 000/5-31-2002/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Cellegy Pharmaceuticals Inc. 349 Oyster Boulevard, Suite 200, South San Francisco, CA 94080
Manufacturer for drug substance: (b) (4)
Drug product: (b) (4)
Reviewer name: krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: 8-5-2002

Drug:

Trade name: Tostrex
Generic name (list alphabetically): testosterone
Code name:CP601B
Chemical name: 17-B-hydroxyandrost-4-en-3-one.
Androst-4-en-3-one, 17-hydroxy-, (17B)-
CAS registry number:58-22-0
Mole file number: -
Molecular formula/molecular weight: $C_{19}H_{28}O_2$/288.42
Structure:

Relevant INDs/NDAs/DMFs: IND (b) (4); DMF (b) (4)

Drug class: Steroid (Androgen)

Indication: Replacement therapy in male hypogonadism (replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone) i.e., 1) primary hypogonadism and 2) hypogonadotropic or secondary hypogonadism.

Clinical formulation: Dermal toxicity of 2 clinical formulations of testosterone gel, CP601 and CP601 B has been tested. The major difference between CP601 and CP601 B is (b) (4). The composition of the CP601B formulation, which is proposed for commercialization is given below:

Ingredients	% (w/w)
Testosterone	2.0
Propylene glycol, USP	(b) (4)
Ethyl alcohol, (b) (4)	
Isopropyl alcohol, USP	
Oleic acid, NF	
Carbomer 1382	
Trolamine, NF	
Butylated hydroxytoluene, NF	
Purified water, USP	
Total	100.00

Note: Clinical formulation CP601 contains (b) (4) in formulation CP601B. It is dispensed as a 60-gram canister of Tostrex 2%. Each full depression of the canister piston delivers one half g gel (10 mg testosterone applied to skin).

Route of administration: Topical, transdermal. One half the dose of Tostrex (1.5 g gel) should gently be rubbed into an area at least 4 x 6 inches of skin of each inner thigh with finger till dried. When applied to the abdomen, the entire dose should be applied to an area at least 8 x 12 inches.

Proposed use: testosterone replacement therapy.
A daily application of 2, (b) (4) contains approximately 40, (b) (4) mg of testosterone, respectively to be applied daily to skin surface. Approximately 12% of the applied testosterone is absorbed across the skin during a 24-hour period, providing an average systemic input of about 7 mg testosterone/day.
In the clinical studies, the initial proposed dose was 3 g Tostrex applied over 300 cm^2. Dose was adjusted based on 24-hour serum testosterone profile obtained after 14 days of daily Tostrex treatment. In general if testosterone concentrations were within the physiological range, the patients were continued on the 3 g dose; if the testosterone concentrations were above the upper limit of physiological range, it was decreased to 2 g applied over 200 cm^2 and if below the lower limit, the dose was increased to 4 g applied over 400 cm^2. The 24-hour serum testosterone concentration profile was repeated 28 days after dosage adjustment and again at Day 182.

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

OVERALL SUMMARY AND EVALUATION:

Introduction: (b) (4) 2% (testosterone gel) is a clear, colorless hydroalcoholic gel containing 2% testosterone. (b) (4) is supposed to provide continuous transdermal delivery of testosterone for 24 hours following a single application producing circulating serum testosterone concentrations that approximate the physiological range (300-1140 ng/dl) found in healthy men.

Endogenous androgens, including testosterone and dihydrotestosterone are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms of male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression and regression of secondary sexual characteristics. Hypogonadism is also a risk factor for osteoporosis in men.

Safety evaluation: There is no safety concern for testosterone which has been approved as testosterone injection products (testosterone enanthate, testosterone cypionate); as testosterone transdermal systems (Androderm and Testoderm patches); and as topical gel (androgel). All other components of the formulation have been used before in approved products.

Safety issues relevant to clinical use: none

Other clinically relevant issues: none

Conclusions: Pharmacology has no concern regarding the safety of the proposed testosterone gel

Communication review:

Labeling review: The label is essentially similar to that of AndroGel except that results of the potential of testosterone transfer study are to be added.

RECOMMENDATIONS: Based on extensive pre-clinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for proposed testosterone gel, Pharmacology recommends approval of NDA 21-463 for Tostrex.

Internal comments: none

External recommendations (to sponsor): none

Draft letter content for sponsor (if not same as above):

NDA issues: none

Reviewer signature:

Team leader signature [concurrence/non-concurrence]**:**

cc: list:
Original NDA 21-463
HFD-580
HFD-580/A.Jordan/M. Hirsch/K. Raheja/F. De-Guia

Memorandum of non-concurrence (if appropriate, attached)**: -**

Addendum to review (if necessary)**: -**

Studies reviewed within this submission: The following toxicity studies conducted by (b) (4) in accordance with GLP regulations have been reviewed:

1. Primary skin irritation potential of active and placebo formulations in rabbits (b) (4) Report number X9B149G
2. Primary skin irritation potential of active and placebo formulations in rabbits. (b) (4) Report number X9C441G
3. Primary skin irritation potential of active formulation in rabbits (b) (4) Report number X01332G
4. Dermal sensitization potential of active and placebo formulations in guinea pigs. (b) (4) Report number X9B150G
5. Dermal sensitization – Buehler method. (b) (4) Report number X1E270G

Studies <u>not</u> reviewed within this submission: No other studies were submitted

Introduction and drug history: as described under Overall summary and evaluation

TABLE OF CONTENTS

PHARMACOLOGY:
None submitted

SAFETY PHARMACOLOGY:

Neurological effects: none submitted

Cardiovascular effects: none submitted

Pulmonary effects: none submitted

Renal effects: none submitted

Gastrointestinal effects: none submitted

Abuse liability: none submitted

Other: local tolerance studies reviewed under toxicology

PHARMACOKINETICS/TOXICOKINETICS:
None submitted

TOXICOLOGY:
No general toxicity studies are submitted. Only local tolerance studies were conducted with the proposed clinical formulations, which are summarized below:

Primary skin irritation potential of active and placebo formulations in rabbits. (b) (4) report # S9B149G

Sixteen New Zealand White rabbits (8/s) were used in 4 treatment groups as follows:

Group A (testosterone gel lot # 8H044A, intact site)
Group B (testosterone gel, abraded site)
Group C (testosterone gel placebo lot # 160091, intact site)
Group D (testosterone gel placebo, abraded site)

There was one skin test site per animals, which was either intact or abraded. Test or placebo material was applied onto the test site of each animal at a dose of 100 ul over a 10 cm^2 area. The sample was dried in 30 minutes and then site was covered with gauze held in place by tape and entire trunk wrapped with bandage. The test and placebo material was applied twice a day, 8 +/- 2 hours apart each day for 5 days. Blood was collected prior to first treatment and then 2 hours after last treatment. After each exposure period, the animals were unwrapped and the guaze patches were removed. All treated sites were observed and scored for irritation every 24 hours during treatment (Days 1 – 4) and for 2 additional days after the last dose (Days 5 and 6). Erythema and edema was recorded each day on a scale of 0- 4 and rated as 0 (non-irritating), 0-2 (mildly irritating), 2-5 (moderately irritating) and > 6 (severely irritating)

Results: Mean primary irritation score was 2.2, 2.5. 2.2 and 3.1 for groups A, B, C and D, respectively. Based on these findings, the test and placebo materials applied either on intact or abraded skin sites were considered moderately irritating.
No data on blood analysis was submitted.

Primary skin irritation potential of active and placebo formulatins in rabbits. (b) (4) report # X9C441G

In this study 16 adult male rabbits were used in 3 groups, group A (test article lot # 8H044A), group B (palcebo article lot # 1602091) and group C (untreated controls). There were 6 rabbits each in groups A and B and 4 in group C. Only intact skin sites were used. The dosing regimen and scoring was similar to that used in the above study. Blood was collected as in the above study.
Results: The Primary irritation score was 1.7, 1.7 and 0 for the groups A, B and C, respectively. Based on MPI both test and placebo formulations were considered mildly irritating.
Blood analysis data was not submitted.

Primary skin irritation potential of active formulation in rabbits. (b) (4) report # X01332G.

In this study 6 young adult rabbits were used. The test article was applied at one site on the skin of each animal at a dose of 100 mg (100 ul) over a 10 cm^2 area and then wrapped in gauze as described in studies above. The test article was applied twice daily, 8 +/- 2 hours apart for 5 days. The test sites were cleaned and allowed to dry before application of the next dose. Blood was collected prior to application and then one hour after application on Days 0 and 4. Each site was scored for erythema and edema after removal of gauze on Days 1 to 6

Results: The cumulative primary dermal irritation scores ranged from 1.7 to 2.8 for the 6 rabbits with mean primary irritation score (MPI) of 2.0. Based on MPI the formulation was considered mildly irritating.

Dermal sensitization potential of active and placebo formulations in guinea pigs. (b) (4) report # X9B150G.

This test was conducted using modified Buehler patch procedure. Fifty-two Hartley albino guinea pigs were used in treatment groups as shown in table below:

Group	# of animals	Conc. %wt/vol	Induction phase			Challenge phase		
			Duration hours	site	# exposures	Conc. %wt/vol	Duration hours	site
Test group	20	2.0	6	R	3	2.0	6	L
Placebo control group	6	0.0	6	R	3	0.0	6	L
Test naïve control	10	NA	NA	NA	NA	2.0	6	L
Positive control	6	0.1	6	R	3	0.025	6	L
Naïve positive control	6	NA	NA	NA	NA	0.025	6	L

R= right flank and L= left flank The test material and placebo were dosed as a gels. A positive control solution of dinitrochlorobenzene (DNCB) was dosed as a solution in 9.5% aqueous ethanol.

In the induction phase, the test and placebo control groups received a volume of 0.15 ml of the test or placebo control materials, respectively. The positive control group received 0.1% solution of DNCB in a volume of 0.3 ml. These were applied on Days 0, 7 and 14 on same site in Hill Top chambers to shaved skin on the right side of the animal and were covered with guaze. Patches were removed after 6 hours and 24 hour after each exposure, the sites were scored for erythema and edema.
In the challenge phase, performed 14 days after the induction exposure, the test, placebo and positive control solutions were administered in Hill Top chambers in the same manner as in the induction exposure, but applied on previously unexposed site the left side of each animal. After a 6 hour exposure, the patches were removed and sites were scored 24 and 48 hours after the dose application. The scoring system was 0 (no reaction), 0.5 (slight patchy erythema, 1 (slight confluent or moderate patch erythema), 2 (moderate erythema) and 3 (erythema, edema, or cracking of the skin).
The results were expressed as incidence score which represents the number of animals in each group showing responses of 1 or greater, at either 24 or 48 hours, expressed as function of the total number of animals tested in the group. The highest possible value for the incidence score is 1.0.
Also severity index was calculated as sum of the test grades for animals in a group, at either 24 or 48 hours, divided by the total number of animals in that group. The highest possible values for the severity index is 3.0.

A primary irritancy screen was run using 4 guinea pigs for the test material to find suitable doses for the induction and challenge phases using the dosing schedule given in table below:

Group	# of animals	Conc (mg/cm^2	Vol (ml/3 cm^2)	Duration (hr)	# of dose sites	Location of sites
Test group	4	5	0.015	6	4	LCr
		10	0.030			RCr
		50	0.150			LCa
		100	0.300			RCa

LCr=left cranial RCr= right cranial
LCa= left caudal RCa= right caudal

The dose chosen for induction was one that did not cause injury to the skin. The dose chosen for the challenge was the highest non-irritating dose, which was considered to be a dose which produced no more than two scores of 0.5 on four animals tested. Based on test screen, the test group was dosed with 0.15 ml volume (50 mg/cm^2)

Results:
Incidence score for the test groups, naïve controls and placebo controls were 0.0 (0% incidence). For positive control group, incidence score were 1.0 (100% incidence) for both the 24 hur and 48 hour observations.
The severity index scores for the test group and the control groups were 0.2 or less. The scores for the positive control were 1.3 for both the 24 and 48-hour observations.
Animals showed no toxic signs during the course of the study.

It was concluded that the test material does not have a potential to be a contact sensitizer in guinea pigs.

Dermal sensitization – Buehler method. (b) (4) report # XIE270G.

This study was repeat of the above study except that Hill Top chambers for the test and placebo articles were to protect the sites but not provide occlusion. They were prepared by removing the webril patch and punching a hole in the top of the chamber with ¼ inch arch punch.
As in the above study results of this test indicated that the test article does not have the potential to be contact sensitizer in Hartley guinea pigs.

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				

Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

GENETIC TOXICOLOGY:
None submitted

CARCINOGENICITY:
None submitted

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:
None submitted

SPECIAL TOXICOLOGY STUDIES:
None submitted

ADDENDUM TO REVIEW:
(if necessary)

APPENDIX/ATTACHMENTS:
none

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/s/

Krishan L. Raheja
8/13/02 01:15:16 PM
PHARMACOLOGIST

Alexander W. Jordan
8/14/02 09:45:25 AM
PHARMACOLOGIST